# Risk of acute myocardial infarction and related medical care receipt in people with serious mental illness

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# RISK OF ACUTE MYOCARDIAL INFARCTION AND RELATED MEDICAL CARE RECEIPT IN PEOPLE WITH SERIOUS MENTAL ILLNESS

**by**

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# ABSTRACT

***Background:***

People with serious mental illness (SMI, including schizophrenia and bipolar disorder) experience adverse health and premature mortality. Higher incidence and/or worse outcome of acute myocardial infarction (AMI) may partly underlie this.

***Objectives*:**

1. To investigate the relative risk of AMI in adult patients with SMI
2. To compare receipt of invasive coronary intervention, inpatient mortality, and recurrence of cardiovascular diseases following AMI between patients with and without SMI
3. To investigate the association between AMI and recent antipsychotic exposure among people with SMI

***Design*:** Historic cohort study for the first two objectives and a case-crossover design for the third objective.

***Setting*:** The Taiwan National Health Insurance Research Database (NHIRD).

***Participants*:** For the first two objectives, adult patients with diagnoses of schizophrenia or bipolar disorder were compared to general population controls. For the third objective, a 'case-crossover design' was utilized, with antipsychotic exposures compared between a 'case period' (proximal to the index AMI) and a 'control period' (more distal to the index AMI).

***Main Outcome Measures*:** Adjusted hazard ratios of AMI were calculated using Cox regression. Invasive coronary interventions and outcomes were compared in logistic regression models. Odds of antipsychotic exposure in case and control time periods were compared within individuals using conditional logistic regression models.

***Results*:** Overall, no increased risk of AMI was found in people with SMI, apart from in sub-group analyses (suggesting an excess SMI-associated risk in younger women). Patients with schizophrenia and bipolar disorder were less likely to receive invasive coronary interventions following AMI episode compared to controls, and inpatient mortality was higher in patients with schizophrenia compared to controls. AMI was significantly associated with more recent antipsychotic exposure in schizophrenia but not in bipolar disorder.

***Conclusion*:** Schizophrenia and bipolar disorder were only associated with raised risk of AMI in young women, but post-AMI care was less adequate in both conditions. A short-term risk of AMI following antipsychotic exposure in schizophrenia was suggested.

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# CHAPTER 1

# INTRODUCTION: SERIOUS MENTAL ILLNESS AND GENERAL HEALTH

### 1.1 Serious Mental illness

The term "serious mental illness" (SMI) was initially defined and measured by the Substance Abuse and Mental Health Services Administration (SAMHSA) in 1996 for the purpose of investigating the prevalence, characteristics, and utilization of mental health treatments in people with SMI and/or those with co-occurring substance use disorders among all persons aged 18 or older (Epstein, 2004). Criteria for SMI were first addressed in the National Survey on Drug Use and Health conducted by SAMHSA and were listed as follows (SAMHSA, 1993; Kessler et al., 2003):

- 'A mental, behavioral, or emotional disorder (excluding developmental and substance use disorder),
- Diagnosable currently or within the past year,
- Of sufficient duration to meet diagnostic criteria specified within the 4th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)(APA, 1994),
- Resulting in serious functional impairment, which substantially interferes with or limits one or more major life activities' (NIMH, 2008).

In 2003, the prevalence of SMI was 9.2 percent among the population aged 18 or older in the United States (SAMHSA, 2003). Disorders encompassed within these criteria were estimated to account for 14% of the burden of disease world wide, and up to half of all disability-adjusted life-years (the sum of years lived with disability and years of life lost) (Mathers & Loncar, 2006; Murray & Lopez, 1996; Prince et al., 2007).

Different studies have included different mental disorders such as schizophrenia, schizoaffective disorder, bipolar disorder, and/or major depressive disorder ((Chang

et al., 2010; Chang et al., 2011; Hayes et al., 2012; Kessler et al., 2003; Kessler et al., 2001; Wang et al., 2002) into definitions of SMI. In this thesis, diagnoses of schizophrenia and bipolar disorder were investigated specifically within this category as the major component mental disorders, following the majority of research in this field, and because they both typically involve psychosis, tend to be more chronic and severe, and require high levels of care due to mental or physical consequences (Chang et al., 2010; Hayes et al., 2012; Kessler et al., 2003).

Schizophrenia is a debilitating mental disorder of the brain with characteristic symptoms of auditory hallucinations, bizarre or paranoid delusions, or disorganized speech or thinking for at least one month. Bipolar disorder is characterized by episodes of mood swings alternate from baseline to mania or depression. For a formal diagnosis, a person with schizophrenia or bipolar disorder must be experiencing significant impairment in their social, interpersonal, or occupational functions for at least six months. There are about 24 million people suffering from schizophrenia (WHO, 2001), and 27 million people with bipolar disorder worldwide (WHO, 2003). Lifetime prevalences have been estimated as 0.3 to 0.7% for schizophrenia (van Os & Kapur, 2009) and 2 to 5% for bipolar disorder (Ketter, 2010).

Schizophrenia and bipolar disorder have been estimated to result in 2.3~2.8 % of the total 'years lost due to disability (YLD)', respectively ranking fifth and seventh in men, and sixth and eighth in women, with respect to the ten leading global causes of YLD in 2004 (WHO, 2008a). They are associated with more severe disability: bipolar disorder has a disability class of V, and active psychosis due to schizophrenia or schizoaffective disorder fall into the most severe class of VII on the Disability classes for Global Burden of Disease study (WHO, 2008a). Moreover, people with

these disorders have a reduced life expectancy compared to the general population (Brown, 1997), and are more likely to suffer from a range of physical disorders including respiratory diseases, infectious diseases, digestive diseases and cardiovascular diseases (Dickey et al., 2002; Oud & Meyboom-de Jong, 2009), as well as being less likely to receive standard care (Bradford et al., 2008; Desai et al., 2002; Kisely et al., 2007; Oud & Meyboom-de Jong, 2009).

## 1.2 Excessive mortality due to natural causes in people with SMI compared with the general population

People with SMI experience significant functional decline and premature mortality (Kisely et al., 2005; Murray & Lopez, 1996). Recent literature has demonstrated significantly increased overall mortality in people with SMI with mortality rate ratio ranging from 1.74 to 2.57 (Kisely et al., 2005; Lawrence D et al., 2000). In addition, excess mortality for specific causes of death has been reported, including that from cardiovascular diseases, with standardized mortality ratios ranging from two- to six-fold excess risk (Kamara et al., 1998; Osby et al., 2001; Osby et al., 2000; Rasanen et al., 2003; Valenti et al., 1997), as well as coronary heart disease (adjusted hazard ratios (HRs) ranging from 1.04 to 2.88 across different age groups), and stroke (adjusted HRs ranging from 1.33 to 2.39 across different age groups) (Osborn et al., 2007).

Considering specific diagnoses within SMI, research worldwide has consistently found that people with schizophrenia have two to three times higher mortality rates for almost all causes of death (Allebeck & Wistedt, 1986; Babigian & Odoroff, 1969; Berren et al., 1994; Brown, 1997; Felker et al., 1996; Harris & Barraclough, 1998; Koranyi, 1979; M et al., 2011; Mortensen & Juel, 1990, 1993; Newman & Bland, 1991; Saha et al., 2007; Tsuang & Simpson, 1985; Tsuang et al., 1980). It is estimated that schizophrenia is associated with a 20% reduction in life expectancy (which translates to a 13 years of shortened life expectancy) compared with the general population (Chang et al., 2011; Hennekens et al., 2005). Although SMI is associated with a raised risk of unnatural causes of death, such as suicide (Brown, 1997), deaths from natural causes have been estimated to be responsible for eighty percent of deaths in people with schizophrenia: about 1.4 times higher than expected (Harris & Barraclough, 1998), and account for about 59% to 62% of the excess

mortality compared with general population (Brown, 1997; Harris & Barraclough, 1998). A meta-analysis of 9 studies published between 1982 to 1993 (encompassing a total population of nearly 6000) estimated that the standardized mortality ratio (SMR) from natural causes of death was 134 (95% CI: 131~137) (Brown, 1997). An SMR within a similar range (SMR=137, 95% CI: 134~141) was estimated in another meta-analysis based on 20 studies published from 1973 to 1995 (Harris & Barraclough, 1998). Although the distributions of causes for these natural deaths in people with schizophrenia were broadly similar to general population, the SMRs for particular causes have been found to be significantly higher. For instance, the SMR for infectious disease mortality was 944 (95% CI: 851~1045) for schizophrenia; those for respiratory disease mortality ranged from 226~230; that for gastrointestinal disease mortality was around 185; that for cardiovascular or circulation disease mortality was 104~110. However, SMRs for neoplastic disease mortality have either not been found to be significantly elevated, or have been found to be significantly lowered in men (Brown, 1997; Harris & Barraclough, 1998).

Much less research has investigated mortality associated with bipolar disorders or affective psychosis compared to schizophrenia. A meta-analysis based on 6 studies of bipolar disorder with a total population size of over 4500, reported an associated SMR of 150 (95% CI: 137~164) for natural death, accounting for 46% of the excess death compared with general population (Harris & Barraclough, 1998). The main causes of excess mortality from natural deaths were respiratory diseases (SMR: 1034, 95% CI: 213~3023) and circulatory diseases (SMR: 158, 95%CI: 139~180).

### 1.3 Worse general health in SMI and reasons

The excess mortality from natural causes in people with SMI may be explained by a higher prevalence of physical comorbidities than in the general population (Hennekens et al., 2005; Kisely et al., 2005; Laursen et al., 2007; Lawrence DM et al., 2003; Osby et al., 2001; Roshanaei-Moghaddam & Katon, 2009). A wide range of studies have confirmed this with respect to different physical disorders including cardiovascular disease, infectious diseases, diabetes, respiratory diseases, and some forms of cancer (Jeste et al., 1996; Kilbourne et al., 2004), with prevalence of physical illness ranged from 9~74% in people with SMI, much higher than the general population (Oud & Meyboom-de Jong, 2009). Odds ratios (OR) for such associations have ranged from 1.1 to 1.8 for cardiovascular diseases (Bresee et al.; Callaghan et al., 2009; Hayward, 1995; Osborn et al., 2007), and 1.8 to 3.8 for diabetes. Other disorders where higher than expected comorbidity has been found with SMI include obesity (1.5~2-fold) (Daumit et al., 2002; Lambert & Newcomer, 2009; Newcomer, 2007), hypertension (1.6-fold) (Goff et al., 2005), malignant neoplasm (1.2~1.4-fold)(Dickey et al., 2002; Lichtermann et al., 2001), gastrointestinal disorders (1.6-fold) (Dickey et al., 2002), HIV (1.4-fold) (Gearon & Bellack, 1999; Stoskopf et al., 2001), dyslipidaemia (5-fold) (Lambert & Newcomer, 2009; Newcomer, 2007), and both acute and chronic respiratory disease (1.2-fold) (Dickey et al., 2002). Most of the above studies either focused on people with schizophrenia (Bresee et al., 2010; Curkendall et al., 2004; Lambert et al., 2003; Lichtermann et al., 2001) or a broader category of psychotic disorder or SMI (Dickey et al., 2002; Osborn et al., 2006). Much less attention has been given into investigation of medical comorbidity in people with bipolar disorder and inconsistent findings have been reported. For instance, some studies have found an elevated risk of cardiovascular diseases in people with bipolar disorder, 1.3~1.6 times higher than that in the general population (Callaghan & Khizar, 2009; Kilbourne et al., 2007);

whereas Lin et al. found no significantly increased risk of acute myocardial infarction (Lin et al., 2008).

Previous research has suggested that such worse physical health in people with SMI might be conceptualized in terms of unwanted events, environmental or economic risks, and health and lifestyle risks (Kilbourne et al., 2006). An example is the relatively high prevalence of respiratory disease in people with SMI. One study found that 15% of people with schizophrenia and 25% of those with bipolar disorder had chronic bronchitis; with 16% and 19% respectively having asthma: all significantly higher than matched controls (Sokal et al., 2004). Such phenomena may reflect the high frequency of smoking or passive smoking among people with mental disorders (Druss et al., 2001a). Another example is cancer in people with SMI. Although studies of lung cancer risk in people with schizophrenia have remained inconsistent in their findings (Brown et al., 1999; Lichtermann et al., 2001; Mortensen, 1994), other research has more consistently found higher risks of digestive and breast cancers associated with schizophrenia (Schoos, 2003), understandable when risk factors of cancer such as tobacco use, unhealthy diet, and physical inactivity, are also known to be more prevalent in people with SMI (Brown et al., 1999; Diaz et al., 2009).

Besides the aformentioned risk health behaviors, recent research has also suggested that people with SMI and physical comorbidity may receive less adequate medical care when judged against clinical standards, with odds ratios for individual recommended preventive physical care or treatments associated with presence of a SMI ranging from 0.35~0.85 (Druss et al., 2001a; Mitchell et al., 2009). However, studies investigating this face substantial methodological challenges. In particular, the prevalence of SMI is quite low, and it is therefore difficult to identify databases

with sufficient numbers of people who have both SMI and a given physical illness to investigate these questions (Cohen et al., 2002).

Of the aforementioned physical comorbidities suggested to have higher prevalence among people with SMI, cardiovascular disease (CVD, a class of disease that involve the heart or blood vessels, with hypertension, ischemic heart disease, coronary heart disease, or acute myocardial infarction as the most common disorders (Harrison's Principles of Internal Medicine 17th Edition, 2008) is already the leading cause of death in the world population. CVD was deemed to be responsible for 29.2% of all deaths in the world (WHO, 2004). Among all CVD, ischemic heart disease (IHD, which includes acute myocardial infarction (AMI), angina pectoris, and heart failure when preceded by AMI) alone accounts for nearly 13% of the total deaths worldwide (7.3 million out of total deaths of 57 million people) (WHO, 2008b). In addition, IHD was estimated to rank 4$^{th}$ among the leading causes of burden of disease, contributing a total of 62.6 million DALYs (Disability-adjusted life years, one DALY representing the loss of the equivalent of one year of full health): 4.1% of the total (WHO, 2008a). While IHD is suggested to cause substantial burden in the general population, reports have also shown that IHD accounts for more than 10% of DALYs in people with SMI (Prince et al., 2007). IHD has also been found to be the major cause of excess mortality in psychiatric patients (Lawrence DM et al., 2003). However, despite the gradual decline in IHD mortality in Australia, droping from 139~209 per 100,000 person-years to 117~143 per 100,000 person-years over the past 20 years, it remained approximately constant (at an average of 280 per 100,000 person-years) in male patients with mental disorders, and has shown an 81 per 100,000 person-years increase in female patients thus affected (Lawrence DM et al., 2003). With higher prevalences of many risk factors of IHD in people with SMI, such as cigarette smoking (Brown et al., 1999; Dixon et al., 1999; Druss et al., 2001a;

Hennekens et al., 2005; Lambert & Newcomer, 2009; McCreadie, 2003; Newcomer, 2007), sedentary lifestyle (Brown et al., 1999), poor diet (McCreadie, 2003), obesity (Fontaine et al., 2001; Manson et al., 1987), hypertension (Collins et al., 1990; Rosner et al., 1977), and hyperlipidemia (Wilson et al., 1998) (Robson & Gray, 2007), and lower receipt of adequate cardiac intervention (Mitchell & Lawrence, 2011), there is a pressing need to understand more about the IHD risk and outcome facts among patients with SMI.

IHD can be categorized into two groups: (1) chronic coronary artery disease (CAD), most commonly presenting as stable angina; (2) acute coronary syndromes (ACS), composed of acute myocardial infarction (AMI) with ST-segment elevation (STEMI) on the electrocardiogram (ECG), unstable angina (UA), and non-ST-segment elevation myocardial infarction (NSTEMI) (Harrison's Principles of Internal Medicine 17th Edition, 2008). Most individuals with IHD show no symptoms or signs until the disease progresses to ischemia, when the blood supply to the tissue fails to meet its demand due to the restriction caused by atherosclerotic plaque on the wall of the blood vessel. AMI occurs when an atherosclerotic plaque ruptures and occludes the coronary artery causing reduced oxygen supply and subsequent tissue death (Cotran RS, 1994; Graham et al., 2007). AMI is diagnosed from complaints of chest pain or discomfort not relieved by rest, findings from the 12-lead ECG, and serum cardiac biomarkers of creatinine kinase-MB (CK-MB) or troponin to distinguish UA from NSTEMI. For patients with ACS, initial treatments should include bed rest, nitrates, beta-blockers, and oral or intra-venous anti-thrombotic therapy. Invasive coronary interventions including coronary arteriography or diagnostic catheterization carried out within 48 hours of admission have been shown to benefit high-risk patients, i.e. patients with multiple clinical risk factors, ST-segment deviation, and/or positive biomarkers. Decisions regarding coronary

revascularization, such as percutaneous transluminal coronary angioplasty (PTCA) or coronary artery bypass surgery (CABG) are then made depending on findings of multiple blockage in coronary arteries investigated by coronary angiography (Harrison's Principles of Internal Medicine 17th Edition, 2008; Van de Werf et al., 2008). Prognosis of AMI depends greatly on the person's own health, the extent of myocardial damage, and the treatments given (Krumholz et al., 2009). However, a meta-analysis of studies encompassing 825,754 individuals concluded that, in people with defined mental disorder, not only is the mortality up to one year after AMI higher than comparison groups (OR = 1.11, 95%CI: 1.00~1.24, p=0.05), but also the receipt of diagnostic and treatment interventions are significantly lower (OR ranged from 0.85~0.87)(Mitchell & Lawrence, 2011).

Moreover, while some of the excess risk of AMI is likely to be explained by adverse lifestyle factors such as smoking and physical inactivity (Robson & Gray, 2007), potential adverse effects of antipsychotic agents have also attracted extensive attention (Brauer et al., 2011; Foley & Morley, 2011). As well as associations with obesity and impaired glucose tolerance as predisposing factors for cardiovascular outcomes (Newcomer, 2004), antipsychotic agents may also have a range of shorter-term adverse cardiovascular effects including QT interval prolongation (Stollberger et al., 2005; Trojak et al., 2006; Vieweg, 2002), ventricular arrhythmia (Gury et al., 2000; Wang et al., 2007), and sudden cardiac death described in schizophrenia (Straus et al., 2004), as well as potential ischemic stroke risk in dementia (Douglas & Smeeth, 2008; Pariente et al., 2012; Rochon et al., 2008). However, research findings in this field are still inconclusive. For instance, Honkola et al.(Honkola et al., 2012) found that use of an antipsychotic was significantly associated with the risk of sudden cardiac death during an acute coronary event, with an OR of 3.4 (95% CI 1.8~6.5) in a case-control study. On the other hand, Osborn et

al. (2007) investigated antipsychotic prescription as a potential mediator but found that this did not explain wholly the elevated risk of cardiovascular diseases, although the association between antipsychotic use and mortality from cardiovascular diseases and stroke was found to show a dose-dependent relationship with hazard ratios ranging from 1.40 to 4.11 (Osborn et al., 2007). A recent systematic review reported a range of both significant and absent associations between antipsychotic exposure and occurrence of AMI among studies in heterogenous clinical settings or using different methodology (Brauer et al., 2011).

### 1.4 Structure of the thesis

The focus of this thesis is on the relationships between schizophrenia, bipolar disorder and acute myocardial infarction (AMI). **Chapters 2~4**, provide a background to the thesis. **Chapter 2** reviews studies investigating the risks of cardiovascular diseases, coronary heart disease, or AMI in people with and without SMI. **Chapter 3** reviews literature on intervention receipt following AMI in people with and without SMI. In **Chapter 4**, literature on studies to date investigating associations between antipsychotic exposure and AMI are summarized. Gaps from literature review, objectives and specific hypotheses of this thesis are described in **Chapter 5**.

**Chapter 6** describes the materials, database, measurements, independent and outcome variables, and processes of data management applied in this study. **Chapters 7~9** then describe in detail the particular statistical analyses used to examine individual hypothesis and summarize the results from the study followed by individual discussion of inferences arising from these. **Chapter 7** describes and compares the risk of AMI in two cohorts of people with and without SMI stratified by age and gender. **Chapter 8** compares the odds of intervention receipt and inpatient mortality following an AMI in people with or without SMI. In **Chapter 9**, associations between AMI and antipsychotic exposure as a potential precipitating factor are investigated. Finally, in **Chapter 10**, the findings from the three preceding chapters are brought together, discussed further, and potential implications are considered.

# CHAPTER 2

# SYSTEMATIC REVIEW ON THE RISK OF ACUTE MYOCARDIAL INFARCTION IN PEOPLE WITH SERIOUS MENTAL ILLNESS

As mentioned in **Chapter 1**, relatively high morbidity and mortality for almost all causes of death have been found in people with serious mental illness (SMI), especially schizophrenia. Although previous research has investigated prevalent cardiovascular or coronary heart disease among people with schizophrenia, the risk of acute myocardial infarction (AMI) in patients with schizophrenia and bipolar disorder is less well documented. The first part of the literature review in this thesis therefore focuses on studies which have compared AMI comorbidity between people with and without SMI.

### 2.1 Search strategy

To encompass all literature comparing incidence of AMI in people with or without SMI, a broad category of cardiovascular or coronary heart disease was included in this review. Individual articles were searched on Pub Med and Ovid Medline using the following search strings:

(Schizophrenia OR bipolar disorder) AND (myocardial infarction OR cardiovascular disease)

or

(Schizophrenia OR bipolar disorder) AND (somatic disease)

or

(Schizophrenia OR bipolar disorder) AND (comorbidity)

or

(Schizophrenia OR bipolar disorder) AND (physical)

(Prevalence OR incidence OR comorbidity) AND (myocardial infarction OR coronary heart disease OR cardiovascular disease) AND (mental illness OR schizo* OR bipolar* OR psych*)

(Astrix '*' in search term searches any ending to the word such as 'psychiatric' or

‘psychotic’; or ‘schizophrenia’ or ‘schizoaffective’).

### 2.2 Selection criteria for studies reviewed

Searches were restricted to studies involving human subjects over 18 years of age; as well as to those carried out in the most recent ten years using large databases (because, since the prevalence of SMI comorbid with AMI is low, large samples are required in order to draw meaningful conclusions). A search for review articles was carried out before searching for individual articles. Two recent reviews were found (Oud & Meyboom-de Jong, 2009; Weiner et al., 2011). Titles of articles identified from Pub Med or Ovid Medline which were not on the reference list of these two review papers were further examined. Due to the large amount of literature obtained from PubMed and Ovid Medline, the custom filter on Pub Med was also used in addition to manual checking to exclude articles that did not match the purpose of search. Abstracts of articles not written in English or Chinese were further examined and excluded if the contents were not relevant to the objective of search. The searches were performed initially in September 2009, with the main database of searches updated in October 2012. Additional articles appearing in the reference lists of papers found from the original search were tracked or located from additional book chapters or conference papers. Full texts of relevant articles were accessed and those that matched the search purpose were summarized.

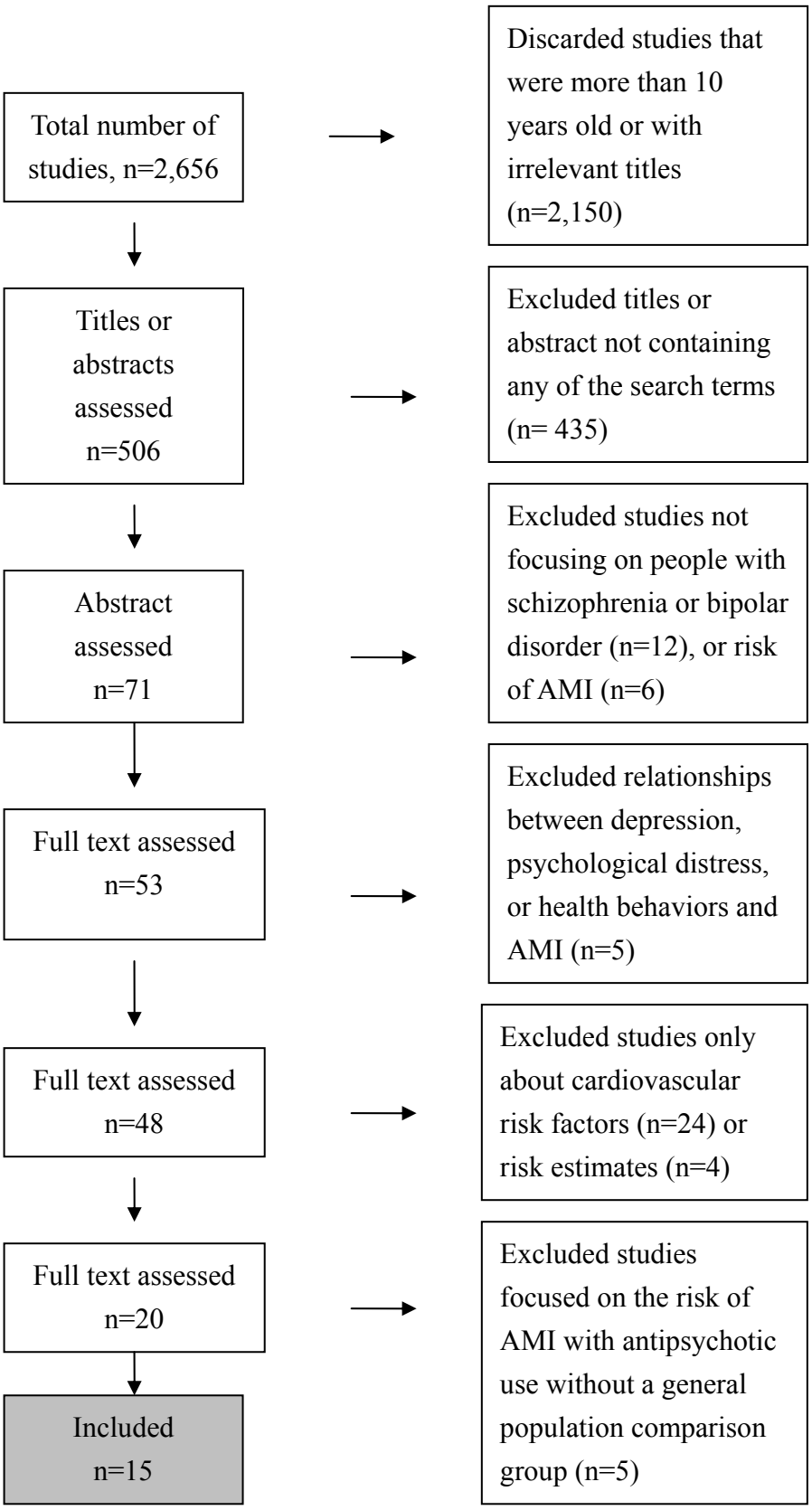
The main outcomes of interest were the odds of prevalence or incidence of an AMI episode expressed as relative risks (RRs), rate ratios, odds ratios (ORs) or hazard ratios (HRs) compared between people with and without SMI. Both crude and adjusted results were taken into account.

Articles that matched the above search string but were not relevant to the objective of this study, and were therefore excluded from this literature review, are categorized and listed as follows:

1. Studies investigating cardiovascular diseases in relation to central nervous system stimulants or tobacco.
2. Reviews or studies not focusing on patients with or without SMI.
3. Studies lacked data on the prevalence or incidence of AMI or coronary heart disease.
4. Studies focused on the relationships between depression, cognitive functions, health behaviors, or quality of life and AMI.
5. Studies focused on the prevalence or incidence of cardiovascular risk factors or levels of blood markers (eg. c-reactive protein or creatinine kinase-MB).
6. Studies focused on risk of AMI with antipsychotic use, but not with serious mental illness.

The systematic reduction of articles was described in **Figure 2.1**.

**Figure 2.1 Flow chart of study selection for literature review**



### 2.3 Search findings

Of the 2,656 articles identified, 2,020 were discarded because they were conducted and published more than ten years ago, did not use large computerized population-based databases, or whose title or abstract did not contain any of the search terms following manual checking and using the custom filter of PubMed. Most of these 2,020 were initially identified because they contained just ‘risk’, ‘morbidity’, ‘prevalence’, OR ‘incidence’; AND ‘somatic’, ‘physical’, OR ‘vascular’; AND ‘illness’. Of the remaining 506 papers, abstracts were assessed and the aforementioned exclusion criteria were applied. A total of 13 studies were included in addition to the two reviews. Fourteen papers compared people with and without SMI. One study focused on the rather broader category of ‘patients with diagnosis of psychosis’ (Truyers et al., 2011). Seven of these papers analyzed specific psychiatric diagnosis of schizophrenia or bipolar disorder. **Table 2.1** further summarises the search results.

**Table 2.1 Studies of acute myocardial infarction (AMI) or coronary heart disease (CHD) among people with SMI (mainly schizophrenia if not specified)**

| **Study, author, and country** | **Sample members** | **Study years; Age or mean age of inclusion;** | **Design of study; Control for confounders** | **Main findings: (adjusted odd ratios (aOR), hazard ratios (HR), or incidence rate ratio (IRR), with 95% confidence interval)** |
|---|---|---|---|---|
| Dickey (Dickey et al., 2002), US | -Total 26,332 Medicaid beneficiaries aged 18~64 in Massachusetts<br>- 11,185 patients has been treated with severe mental illness[2] | - One year prevalence<br>- Mean age: 40 (SD 11) and 32 (SD10) for those with or without mental disorders, respectively | -Cross-Sectional study<br>- Adjusted for age, gender, and race or ethnicity | People with severe mental illness had an increased risk of heart disease with an adjusted odds ratio of 3.19 (95%CI 2.51~4.07) |
| Curkendall (Curkendall et al., 2004), Canada | -3,022 patients with schizophrenia<br>- Four age- and gender- matched controls for each individual | - Mean age: 49.6 (SD 17.8) and 49.6 (SD17.7) for those with or without schizophrenia, respectively | - Cohort study<br>- Prevalence of cardiovascular morbidity during 1994 and 1995<br>- Incidence of cardiovascular morbidity from 1996~1999<br>- Adjusted for age, sex, and medical risk factors | - Associations between schizophrenia and prevalence of AMI: aOR=1.3, 95%CI 0.9~1.9;<br>- Associations between schizophrenia and prevalence of ischemic heart disease: aOR=1.1, 0.9~1.3<br>- Associations between schizophrenia and incidence of AMI: aOR=0.9, 95%CI 0.6~1.4<br>- Associations between schizophrenia and incidence of ischemic heart disease: aOR=1.1, 0.9~1.4 |

| | | | | |
|---|---|---|---|---|
| Goff<br>(Goff et al., 2005),<br>US | -689 Schizophrenia patients recruited from 54 clinical sites<br>- Age and gender matched controls | - Mean age: 40.4 (SD 11.2) and 40.4 (11.2) for those with or without schizophrenia, respectively | - Cohort study<br>- Incidence of CHD morbidity from 1999~2004 | People with schizophrenia had a significantly higher ten-year risk of coronary heart disease in both male (9.4% vs. 7.0%) and female (6.3% vs. 4.2%) compared to controls ($p < 0.001$). |
| Kilbourne<br>(Kilbourne et al., 2007), Canada | - 7,529 male Veteran Administration patients of different psychiatric diagnoses | - Mean age: 54.5 years | - Cross-sectional study<br>- Adjusted for or stratified by age | - People with bipolar disorder were 44% more likely to have CHD than patients with schizophrenia |
| Lin<br>(Lin et al., 2008),<br>Taiwan | -1429 hospitalized patients with bipolar disorder,<br>-Compare with patients receiving appendectomy (n=4993) | -1997~2001<br>-Mean age: 54.8 (SD 9.6) and 60.0 (11.6) for those with or without schizophrenia, respectively | - Cohort study<br>- Adjusted for age and comorbid medical disorders | - OR of developing AMI comparing patients with bipolar disorder and patients receiving appendectomy: aOR= 1.31(0.87~1.97) |
| Callaghan<br>(Callaghan et al., 2009), Canada | - 9,815 patients with schizophrenia<br>- Matched with appendicitis-related diagnoses on sex, age, average neighbourhood income level, and amount of follow-up time available | - 2002~2006<br>- Mean age before matching: 41.0 (SD 14.0) and 38.6 (15.1) for those with or without schizophrenia, respectively<br>- Mean age after matching: 40.3 (SD 13.8) and 40.2 (15.2) for those with or without schizophrenia, respectively | - Cohort study<br>- Adjusted for age, sex, neighbourhood income level, tobacco related-problems, and comorbid medical disorders | People with schizophrenia had a greater risk of readmission for cardiovascular events, with an adjusted hazard ratio of 1.43 (95% CI 1.22~1.69) compared to the appendicitis group. |

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| Callaghan (Callaghan & Khizar, 2009), Canada | - 5,999 patients with bipolar disorder<br>- Matched with appendicitis-related diagnoses on sex, age, average neighbourhood income level, and days from index admission to study end | - 2002~2006<br>- Mean age before matching: 42.9 (SD 15.0) and 38.6 (15.1) for those with or without schizophrenia, respectively<br>- Mean age after matching: 42.0 (SD 14.4) and 42.1 (15.3) for those with or without schizophrenia, respectively | - Cohort study<br>- Adjusted for age, sex, neighbourhood income level, tobacco related-problems, and comorbid medical disorders | People with bipolar disorder had a greater risk of readmission for cardiovascular events, with an adjusted hazard ratio of 1.66 (95% CI 1.36~2.03) compared to the appendicitis group. |
| Laursen (Laursen et al., 2009), Denmark | - 4,997 patients with severe mental disorder[3] from a 4.6 million population cohort | - 1994~2007 | -Cohort study<br>- Adjusted for or stratified by age, and gender | People with severe mental disorder had a slightly increased incidence rate ratios of heart disease at 1.11 (95%CI 1.08~1.14). |
| Lin (Lin et al., 2010b), Taiwan | - 7,353 patients hospitalized with diagnosis of schizophrenia<br>- Matched with 22,059 enrollees from general population on age and gender | - 2000~2006<br>- 47.3% of the sample were <35 years of age | -Cohort study<br>- Adjusted for comorbid medical disorder | People with schizophrenia had a significantly higher risk of AMI (adjusted hazard ratio of 1.83, 1.62~2.05) than the comparison group. |
| Bresee et al (Bresee et al., 2010), Canada | - 28,755 patients identified with schizophrenia<br>- Compared with 2,281,636 control patients without schizophrenia | - 1995~2006<br>- Mean age before matching: 47.6 (SD 16.7) and 45.3 (16.6) for those with or without schizophrenia, respectively | - Cross-sectional study<br>- Adjusted for age, sex, socioeconomic status, and GP visits<br>- Stratified by age and gender | People with schizophrenia had a significant higher risk of acute coronary syndrome (unadjusted odds ratio 1.09, 1.01 ~1.18), ischemic heart disease (1.52, 1.48 ~1.56), and cardiovascular disease (1.76, 1.72~1.81). Risks were different across |

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| | | | | different age groups, with younger groups of people with SMI at higher risk of cardiovascular diseases. |
| Truyer<br>(Truyers et al., 2011), Belgium | - A total of 197,000 patients that covered 1.5% of population from Flanders, north Belgium<br>- 894 patients with diagnosis of psychosis<br>- 4010 non-psychotic controls were matched (1:5) with age (± 5 years), gender, within a practice | - 1994~2007<br>- Mean age at the diagnosis of psychosis: 48.8 (SD 21)<br>- Mean age of control group: 45.5(SD19) | - Retrospective cohort study<br>- Adjusted for age, gender, and frailty model (which characterizes the relationship or dependence of corrected failure times). | - No significant higher risk of cardiovascular disease in people with diagnosis of psychosis, adjusted HR : 1.02 (0.70~1.47) |
| Laursen<br>(Laursen et al., 2011), Denmark | - A total of 2,450,812 persons 15~52 years old, at risk for admission with one of the 19 somatic diseases<br>- 16,079 and 6,215 patients have been in contact with a psychiatric hospital for schizophrenia or bipolar disorder, respectively | - 1995~2006 | - Population-based cohort study<br>- Adjusted for or stratified by gender, calendar time, and age (made in 5-year groups) | - Incidence rates of hospital contacts for AMI were higher (IRR >1) in people with schizophrenia, but not significant in bipolar disorder. (no actual numbers shown in figures) |
| Lahti<br>(Lahti et al., 2012), Finland | - A total of 12,939 people born in 1934~1936, 1940, and 1944 from the Helsinki Birth Cohort Study<br>- 117 men and 87 women were | - Followed up between 1969~ 2002<br>- The median age at first hospitalization for schizophrenia was 35.3 years (SD9.7), and 55.6 years | - Population-based cohort study<br>- Stratified for sex and year of birth;<br>-Adjusted for socio-economic position in childhood, lipid-lowering, and | - Risk of hospitalization for coronary heart disease was significantly higher in people with schizophrenia: adjusted HR: 2.00 (1.25~3.21) |

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| | diagnosed with schizophrenia<br>- 86 men and 96 women were diagnosed with non-schizophrenic psychotic disorder | (7.9) for coronary heart disease | antihypertensive agents, | |

[1]Mainly adapted from Oud et al. (Oud & Meyboom-de Jong, 2009)

[2]Severe mental illness: Dickey et al. selected disabled beneficiaries who had at least one claim for the treatment of schizophrenia, bipolar disorder, or another psychotic disorder (Dickey et al., 2002)

[3]Severe mental disorder: Laurson et al. included patients with bipolar disorder, schizophrenia, and schizoaffective disorder (Laursen et al., 2009)

Search results in this literature review were similar to the two aforementioned reviews (Oud & Meyboom-de Jong, 2009; Weiner et al., 2011). As shown in **Table 2.1**, there were substantial variations in sampled populations, exposure categories, and outcome measures between these studies. Three studies examined risks of cardiovascular diseases within composite groups of patients with diagnoses of psychotic disorder or SMI without further subgroup analysis (Curkendall et al., 2004; Dickey et al., 2002; Laursen et al., 2009; Truyers et al., 2011). Two studies revealed elevated risk of heart disease (Dickey et al., 2002; Laursen et al., 2009) or cardiovascular disease (Callaghan et al., 2009; Callaghan & Khizar, 2009; Truyers et al., 2011) in people with SMI, without mentioning specific risks of AMI or coronary heart disease. One study did not have a control group from general population, and just compared the risk of coronary heart disease between patients with schizophrenia, schizoaffective, and bipolar disorder (Kilbourne et al., 2007). As for outcome measures, most studies described odds ratios or hazard ratios for coronary heart or cardiovascular diseases. One study just described incidence of ten-year risk of coronary heart disease and no odds ratio was calculated (Goff et al., 2005).

Regarding main findings, two studies mentioned excessive risk of heart disease in people with diagnosis of severe mental illness (Dickey et al., 2002; Laursen et al., 2009) with odds ratios or incidence ratios ranged from 1.11~3.19; whereas Truyer et al. found no significant elevated risk of cardiovascular disease in people with diagnosis of psychosis. Most studies reported increased likelihood of AMI (odds ratios 1.09 to 1.83), coronary heart disease (odds ratios 1.43 to 2.00), or cardiovascular disease (odds ratios 1.11 to 3.19) in people with schizophrenia. One study reported elevated risk readmission due to cardiovascular events in bipolar disorder compared to controls (Callaghan & Khizar, 2009). The study that didn't have a comparison group from general population reported a 44% increased

likelihood of coronary heart disease in people with bipolar disorder than in schizophrenia. However, there were three studies other than the aforementioned research from Truyer et al. that found insignificant associations of AMI in people with schizophrenia (Curkendall et al., 2004) and bipolar disorder (Laursen et al., 2011; Lin et al., 2008), respectively. Among these four studies with null associations, Truyers et al. discussed that the surprisingly lower cardiovascular morbidity after psychosis might be due to the relatively short follow-up time before cardiovascular diseases actually emerge (Truyers et al., 2011). Curkendall et al. emphasized that despite insignificant findings in AMI, all the other cardiovascular comorbidies including arrhythmia, heart failure, stroke, and diabetes had significantly higher prevalence and incidence compared to controls (Curkendall et al., 2004). Laursen et al. suggested that the reason for the decreased likelihood of somatic contacts due to heart disease in people with SMI was probably owing to the severity and symptoms of mental disorders. However, Laursen et al. and Lin et al. (Lin et al., 2008) both mentioned that considering the 1.9~3-folds of excessive mortality due to cardiovascular disease being reported in people with SMI (Laursen et al., 2009) or bipolar disorder (Angst et al., 2002; Osby et al., 2001), it is in fact more important to notice the insufficient health contacts or physical care being provided to those people (Laursen et al., 2009; Lin et al., 2008).

Age and gender differences on the risks of coronary heart disease were found following stratification, with women (Bresee et al., 2010; Lahti et al., 2012), or patients of younger age (Bresee et al., 2010; Laursen et al., 2009) reported to be at a particularly high risk. In the study conducted by Laursen et al (2009), elevated incidence rate ratios (IRR) of medical contacts due to overall heart disease were significantly higher in patients with severe mental disorder less than 70 years of age and not in those older than age 70. However, medical contacts due to AMI were not

significantly higher in the same age range. Finally, among the seven papers reporting specific psychiatric diagnoses, most studies found significantly elevated risks of AMI or coronary heart disease comparing patients with and without schizophrenia (odds ratios 1.09~2.00). However, two out of three studies reported no significant relationship with bipolar disorder (Laursen et al., 2009; Lin et al., 2008).

## 2.4 Conclusion

Although studies have found associations of schizophrenia and bipolar disorder with elevated risk of death from cardiovascular disease (see **Chapter 1**), morbidity risks of AMI or coronary heart disease have mostly focused on people with schizophrenia, reporting increased risk compared with the general population. Associations between bipolar disorder and AMI have received much less attention and findings have been inconsistent. All findings to date have predominantly analysed combined samples, rather than looking at modifying effects by age or gender. Only one study has reported elevated risk of cardiovascular disease (but not specifically AMI) in people with schizophrenia across different age groups (Bresee et al., 2010) but did not investigate bipolar disorder. Further investigation on exploring the modification by age and gender on risk of AMI between schizophrenia and bipolar disorder is therefore needed.

Finally, it is important to bear in mind that inclusion or exclusion criteria of this review were just agreed by the candidate and the supervisor and not by two independent raters. In addition, due to the large numbers of articles identified using PubMed or Ovid Medline, selections by custom filter in addition to manual checking were carried out, and only full texts of studies using large database conducted in recent ten years, published in English or Chinese language were obtained and summarized by the candidate. Thus, it should be borne in mind that this literature review did not include relatively old studies, those judged as using too-small samples, and articles in Korean or Japanese (although the candidate did not identify any evidence of important missing literature from East Asia in the process of checking titles and abstracts).

# CHAPTER 3

# LITERATURE REVIEW ON THE INVASIVE CORONARY INTERVENTIONS AND TREATMENT OUTCOME FOLLOWING ACUTE MYOCARDIAL INFARCTION IN PEOPLE WITH SERIOUS MENTAL ILLNESS

Research investigating excess risk of acute myocardial infarction (AMI) in people with serious mental illness (SMI) has been summarized in **Chapter 2**. The objective of the second part of the literature review was to summarize the literature on intervention receipt and treatment outcomes following AMI in this group.

### 3.1 Search strategy

The literature search was carried out on Pubmed and Ovid Medline using the following strings:

(intervention AND receipt) AND (myocardial infarction OR coronary heart disease) AND (mental illness OR schizo* OR bipolar* OR psych*)

or

(catheterization) AND (myocardial infarction OR coronary heart disease) AND (mental illness OR schizo* OR bipolar* OR psych*)

or

(revascularization) AND (myocardial infarction OR coronary heart disease) AND (mental illness OR schizo* OR bipolar* OR psych*)

or

(mortality OR prognosis) AND (myocardial infarction OR coronary heart disease) AND (mental illness OR schizo* OR bipolar* OR psych*)

or

(recurrence) AND (myocardial infarction OR coronary heart disease) AND (mental illness OR schizo* OR bipolar* OR psych*)

or

(second) AND (myocardial infarction OR coronary heart disease) AND (mental illness OR schizo* OR bipolar* OR psych*)

The searches were restricted to studies of human subjects over 18 years of age, and without restrictions on lengths or timing of studies, nor on geographical locations. A search for review articles was carried out before searching for individual articles. One systematic review (Mitchell, 2009) and one meta-analysis (Mitchell & Lawrence, 2011) were found (Oud & Meyboom-de Jong, 2009; Weiner et al., 2011). Titles of articles identified from PubMed or Ovid Medline which were not on the reference list of these two review papers were further examined. Abstracts of articles not written in English or Chinese language were further examined and excluded if the contents were not relevant to the objective of search. The searches were performed initially in January 2010, then updated in September 2012. Full texts of relevant articles were accessed and those that matched the search objectives were summarized.

### 3.2 Selection criteria of studies

Studies that reported intervention receipt or treatment outcome following AMI in patients with SMI were included. Of the standard post-AMI interventions mentioned in **Chapter 1**, invasive coronary interventions were chosen as the main search outcomes in this literature review because most literature focused on these (Mitchell & Lawrence, 2011) and investigation of these interventions was considered to be most feasible in the study to be described. In terms of outcome following AMI, studies were reviewed which compared mortality or recurrence following an AMI episode in people with or without SMI. Crude and adjusted results expressed as relative risks (RR), rate ratios, odds ratios (OR) or hazard ratios (HR) were studied.

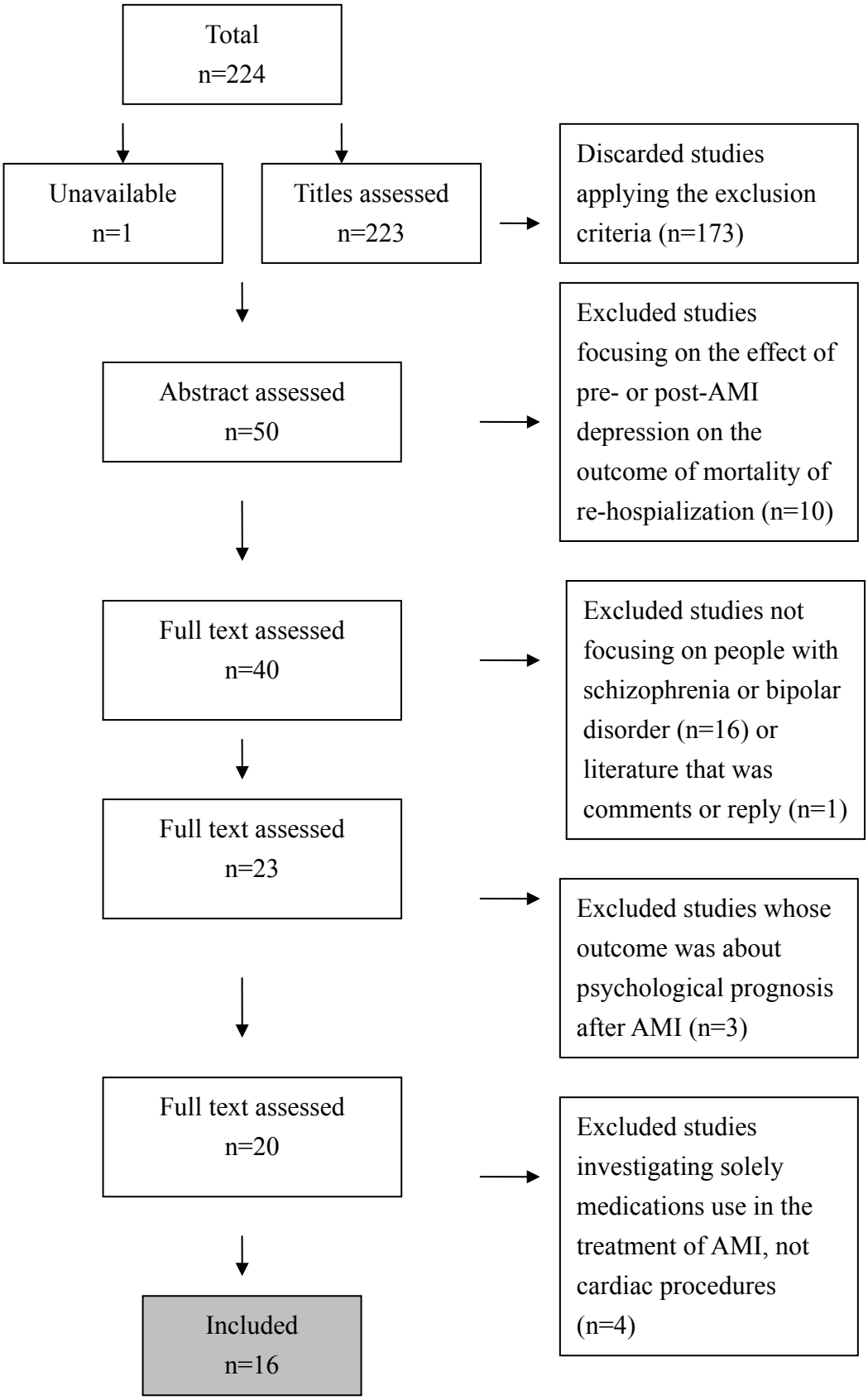
The following exclusions were applied:

1. Comments or author's reply.

2. Studies exclusively investigating depression, cognitive functions, or quality of life as outcomes.
3. Studies of mortality or recurrence of AMI just among general population but not those with schizophrenia or bipolar disorder.
4. Studies lacking a non-psychiatric comparison group.
5. Studies of cardiac rehabilitation (e.g. exercise programmes, health education, or counseling sessions offered to survivors of AMI) or those which compared the efficacy or safety profiles of pre- or post-operative statin use.
6. Studies evaluating levels of blood markers (e.g. c-reactive protein or creatinine kinase-MB) without assessing the delivery of medical services.
7. Studies solely focused on cardiovascular medications as outcomes (eg. aspirin, anticoagulant, antihypertensive) rather than invasive coronary procedures.

References of related articles were scrutinized and potentially relevant publications that were not included in the original search were accessed. The systematic selection of articles is described in **Figure 3.1**.

**Figure 3.1 Flow chart of selecting the studies**



### 3.3 Summary of search findings

Of the 224 papers that were initially identified using the search strings, 208 were excluded applying the aforementioned criteria. Among the remaining 16 papers, there was one systematic review of the quality of medical care on general internal medicine, cardiovascular, diabetes, infection, and cancer for people with or without mental illness (Mitchell et al., 2009) which reviewed ten studies, examining a broad category of cardiac care (including pharmacotherapy and invasive coronary interventions), and found seven out of ten reporting lower quality of care in people with mental illness. Another meta-analysis specifically focused on invasive coronary interventions treatments and mortality following acute coronary syndrome in people with mental disorders (Mitchell & Lawrence, 2011) (as summarized in **Table 3.1**). The other fourteen studies compared likelihood of intervention receipts in people with and without mental disorder. Among them, six analyzed subgroups with schizophrenia or affective disorder.

Results comparing receipt of cardiovascular procedures and mortality following AMI between people with or without mental disorder have been inconsistent. Reasons for inconsistencies have been suggested to include variations in study populations and health care systems sampled (Kisely et al., 2009). As shown in **Table 3.1**, reduced likelihood of catheterization or revascularization (67~90% odds of receipts compared with those in the general population) in people with mental disorder have been reported, mostly focusing on people aged 65 years or over, and using large databases such as the US Medicare system (Druss et al., 2000; Druss et al., 2001a), the Healthcare Investment Analysts (HCIA) Sachs Projected Inpatient database (Young & Foster, 2000), or Veteran Health System in the US (Petersen et al., 2003); as well as 35~92% reduced likelihood in studies using population-based health services research databases in West Australia (Lawrence DM et al., 2003), Canada (Kisely et

al., 2009), and Denmark (Laursen et al., 2009). However, there were also some studies that have found no significant differences in intervention receipt in people with or without mental illness using the US Veterans Health Administration (Abrams et al., 2009; Plomondon et al., 2007), the US Medicaid claims (Jones DR et al., 2004), or New York Sate hospital discharge records (Li et al., 2007), although these have tended to have smaller sample sizes.

**Table 3.1 Summarizing studies comparing medical care receipt and outcome following AMI in people with or without SMI**

| **Study, author, and country** | **Sample members** | **Study years; Age or mean age of inclusion; Control for confounders** | **Principal findings on procedure receipt in people with <u>any</u> mental disorder compared to the general population** | **Principal findings on procedure receipt in people with <u>specific psychiatric diagnoses</u> compared to the general population** | **Revascularization among those undergoing catheterization** | **Outcomes of mortality or AMI recurrence** |
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| Druss (Druss et al., 2000); US | -Patients over 64 years of age from Medicare with confirmed diagnosis of AMI<br>-5,365 patients with mental disorder<br>-108,288 patients without mental disorder | - Patients were hospitalized for AMI between February 1994~July 1995<br>-Mean age: 79.5 (SD 6.9) years;<br>-Controlled for demographic, clinical, hospital, and regional variables | People with <u>any</u> mental disorder were significantly <u>less</u> likely to undergo:<br>- Catheterization (RR 0.72*[2])<br>- PTCA[3]: (RR 0.75*)<br>- CABG[4]:(RR 0.68*) | People with <u>schizophrenia</u> and <u>affective disorders</u> were significantly less likely to undergo:<br>- Catheterization: RR 0.41* for schizophrenia; 0.65* for affective disorder;<br>- PTCA : RR 0.55** for schizophrenia; 0.51** for affective disorder;<br>- CABG:RR 0.27* for schizophrenia; 0.63** for affective disorder | No significant difference between people with or without mental disorders (p=0.12 for PTCA; p=0.06 for CABG), schizophrenia (p=0.36 for PTCA; p=0.08 for CABG), or affective disorder (p=0.07 for PTCA; p=0.12 for CABG) | No significant difference in the likelihood of 30-day mortality adjusted for all variables including PTCA and CABG for:<br>- Any mental disorder: p=0.22;<br>- Schizophrenia: p=0.18;<br>- Affective disorder p=0.20. |
| Young (Young & | -354,195 patients with diagnosis of AMI | - 1998<br>- 40.5% of patients were | People with any mental disorders were significantly | People with <u>schizophrenia</u> and <u>affective disorders</u> were | Not mentioned | - In the subgroup aged 65 years and older, people |

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| Foster, 2000); US | from Healthcare Investment Analysts (HCIA)<br>-25,237 patients with mental illness<br>-328,958 patients without mental disorder | younger than 65 years<br>- Stratified by younger and older age groups<br>- Unable to adjust for admission characteristics or left ventricular function | less likely to undergo:<br>(1) Age >=65 years:<br>- catheterization: RR=0.77, 95% CI(0.75~0.80)<br>- PTCA : 0.68 (0.65~0.72) ;<br>- CABG : 0.67 (0.62~0.72)<br>(2) Age <65 years :<br>- catheterization : 0.88 (0.86~0.90)<br>- PTCA: 0.70 (0.68~0.73)<br>- CABG: 0.79 (0.75~0.84) | significantly less likely to undergo:<br>(1) Age >=65 years:<br>- Catheterization: RR=0.51 (0.42~0.62) in schizophrenia; 0.80 (0.71~0.88) in affective disorder;<br>- PTCA : 0.32 (0.21~0.47) in schizophrenia; 0.78 (0.65~0.92) in affective disorder;<br>- CABG: 0.67 (0.46~0.95) in schizophrenia; 0.61 (0.47~0.80) in affective disorder;<br>(2) Age<65 years:<br>- Catheterization: 0.70 (0.63~0.77) in schizophrenia; 0.93 (0.87~0.99) in affective disorder;<br>- PTCA: 0.55 (0.46~0.65) in schizophrenia; 0.79 | | with mental illness have 21% lower risk-adjusted likelihood of death compared with the reference group (p<0.001).<br>- In the subgroup of younger than 65 years of age, people with schizophrenia have an 86% increased risk-adjusted likelihood of death (p<0.001) |

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| | | | | (0.70~0.88) in affective disorder;<br>- CABG: 0.71 (0.54~0.92) in schizophrenia; 0.78 (0.62~0.97) in affective disorder. | | |
| Druss (Druss et al., 2001a); US | -88.241 patients over 64 years of age from Medicare with confirmed diagnosis of AMI<br>- 4,664 patients with mental disorder<br>- 108,288 patients without mental disorder | -Patients were hospitalized for AMI between February 1994~July 1995<br>- Mean age: 76.0 (SD 7.3) and 76.1 (SD7.1) for those with or without mental disorders, respectively<br>- Controlled for demographic characteristics, cardiac risk factors, cardiac history, admission characteristics, and left ventricular function | -Patients with mental disorder were <u>less</u> likely to receive reperfusion therapy: 0.74 (95%CI 0.56~0.95)* | -Patients with schizophrenia were less likely to receive reperfusion therapy: 0.52 (0.26~0.90)<br>- Patients with affective disorder were less likely to receive reperfusion therapy: 0.71 (0.45~0.99) | | - Patients with any mental disorder had an increased likelihood of mortality compared to rest of the population during the year after hospital discharge: HR 1.19 (1.04~1.36)<br>- Patients with schizophrenia (compared to the rest of the population): HR 1.34(1.01~1.66)<br>- Patients with affective disorder: HR 1.11(1.03~1.18) |

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| | | | | | | - But in the model adjusting for quality measures and all covariates, the associations between mental disorder and 1-year mortality was no longer significant (p=0.17); similar for schizophrenia: HR 1.23 (0.96~1.26); affective disorders: HR 1.05 (0.87~1.23) |
| Lawrence (Lawrence DM et al., 2003); Australia | - 44,767 deaths due to ischemic heart disease (IHD) from the West Australia Linked Database (population-based)<br>- 3796 deaths occurred in users of mental health services | - 1980~1998<br>- Unable to adjust for demographic and clinical characteristics | | People with schizophrenia and affective psychosis were significantly less likely to undergo revascularization:<br>- Schizophrenia, male: 0.31 (0.21~0.45); female:0.34 (0.18~0.64)<br>- Affective psychosis, male:0.77 (0.64~0.93); female: 0.79 | Not mentioned | |

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| | - 59% were ascribed to acute myocardial infarction | | | (0.62~1.01) | | |
| Petersen (Petersen et al., 2003); US | - Patients treated for AMI from Veterans Health Administration<br>- 859 patients with mental illness<br>- 3,481 patients without mental illness | - January 1994~September 1995<br>- Mean age: 63.0 (SD 12.0) in the SMI group; 66.5 (10.2) in the non-SMI group<br>- Adjusted for age | People with any mental disorders were significantly less likely to receive<br>- diagnostic angiography:0.90 (0.83~0.98)<br>- PTCA: 0.92 (0.76~1.11)<br>- CABG: 0.80 (0.60~1.07) | | Not mentioned | - 30-day mortality: 0.80 (0.47~1.35)<br>- 1-year mortality: 1.26 (0.94~1.68) |
| Jones (Jones LE & Carney, 2005); US | - Patients aged 18~64 hospitalized for AMI from the Blue cross/ Blue Shield of Iowa administrative claims data (Medicaid)<br>- 1,342 patients with mental disorder<br>- 2026 without mental disorder | - 1996~2001<br>- Mean age: 53.4 (SD7.7) in the SMI group; 54.8 (7.4) in the non-SMI group<br>- Controlled for age, gender, number of days hospitalized, residence (rural, urban), hospital transfer, cardiovascular risk factors, and other | The odds ratio for receiving PTCA and CABG were not significantly different in people with any mental disorders compare with general population (odds ratio for receiving PTCA: 1.10 (0.95~1.29); CABG 0.89 (0.71 ~ 1.11) | | - Significant predictors of demographic variables and specific cerebro- or cardiovascular conditions.<br>- Age, gender, and race were not significantly different across the antipsychotic groups | |

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| | | medical comorbidity (Elixhauser Comorbidity Index) | | | | |
| Kisely (Kisely et al., 2007); Canada | - Identified from Nova Scotia's Mental Health Outpatient Information System<br>- 17,665 deaths from circulatory disease<br>- 2,839 were people with psychiatric problems | - January 1, 1995 and December 31, 2001<br>- Adjusted for principal psychiatric diagnosis, age, sex, social economic status, treatment setting, residence and medical comorbidity | People with any mental disorder were significantly less likely to receive catheterization (RR 0.92, 95% CI 0.86 ~0.98); but not PTCA (0.97, 0.86 ~1.09), CABG (0.92, 0.83~1.02).<br>- | Note: Psychiatric hospital inpatients had significantly lower rate ratios of receiving same procedures than patients from outpatient settings.<br>Adjusted rate ratios for inpatient vs. outpatient settings respectively:<br>- Catheterization :0.41 (0.26~0.65) vs .0.56 (0.44~0.70);<br>- PTCA: 0.22 (0.07~0.69) vs. 0.59 (0.39~0.89)<br>- CABG: 0.34 (0.15~0.77) vs. 0.66 (0.47~0.93) | | For first hospital admissions (mostly due to ischemic heart disease), the age-standardized rate ratio of deaths was 1.34 (1.32~1.37).<br>- Significantly higher for patients treated under specialist services (1.74, 1.68~1.81) vs. primary care (1.29, 1.26~1.31)<br>- Rate ratios in patients with nonaffective psychoses: 2.11 (1.93~2.30)<br>- In patients with mood disorder: 2.01 (1.76~2.35) |

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| Li (Li et al., 2007); US | - Total 39,839 patients receiving CABG<br>- 3,211 patients had diagnosis of any mental disorder<br>- 36,628 patients without diagnosis of mental disorder | - 2001~2003<br>- Mean age: Patients with psychiatric disorder: 67.5 (SD 11.2); Patients without: 67.1 (10.8)<br>-Controlling for individual demographic, socioeconomic, clinical characteristics, and surgeon work volume | - Patients with mental illness had an odds of 1.28* for receipt of care from a high mortality surgeon.<br>- No evidence suggests that these patients are disadvantaged in access to high-quality cardiac surgeons | | Not measured | |
| Plomondon (Plomondon et al., 2007); US | - 14,194 patients with acute coronary syndrome presenting to Veterans Health Administration<br>- 2,623 patients had a diagnosis of serious mental illness (SMI)<br>- 11,571 patients without | - October 2003~September 2005<br>- Mean age: 64.0 (SD 11.7) and 69.6 (11.5) for patients with or without SMI, respectively<br>- Adjusting for demographic, cardiac, and non-cardiac comorbidieis, presentation factors, in-hospital procedures and discharge medications | No significant difference between people with or without SMI in the rates of receipt of:<br>- Diagnostic catheterization: p=0.14 ;<br>- Percutaneous coronary interventions: p=0.10<br>- CABG: p=0.61 | | | Between people with or without SMI, the following outcomes were not significantly different after adjustments:<br>- 1-year all- cause mortality: HR 0.91 (95%CI 0.81~1.02)<br>- The combined endpoint of all-cause mortality and re-hospitalization for AMI: in people with |

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| | | | | | | any SMI: HR 0.99 (0.90~1.10); in people with schizophrenia: HR 0.83 (0.60~1.15); in people with mood disorder : HR 0.91 (0.68~1.5)<br>- |
| Abrams (Abrams et al., 2009); US | - 21,745 patients admitted to Veterans Health Administration with AMI<br>- 5,887 patients were identified as having psychiatric diagnosis | - 2004~2006<br>- Mean age: 68.5 (SD 11.6)<br>- Adjusted for age, race, gender, marital status, VHA eligibility criterion, comorbid medical condition, mechanical ventilation on day of admission, location of infarction, and 9 selected lab results within 48 hours of admission time. | Patients with psychiatric comorbidity had <u>lower</u> receipt of revascularization based on:<br>- outpatient codes: 0.92( 0.85 ~ 0.99)<br>- but similar receipt based on inpatient codes 1.00 ( 0.91 to 1.10). | | | Patients with psychiatric comorbidity had higher adjusted 30- and 365-day mortality, based on<br>- outpatient psychiatric codes , with odds ratios 1.19 (95% CI, 1.09 ~ 1.30), and 1.12 (1.03~ 1.22), respectively;<br>- but similar mortality based on inpatient codes: 0.89 (0.69~ 1.01) and 0.93 (0.82 ~ 1.06), respectively). |

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| Laursen (Laursen et al., 2009); Denmark | - All persons born in Denmark before January 1, 1994 from the Danish Civil Registration System<br>- Among the 605, 649 patients who had a diagnosis of heart disease, 4,997 persons had diagnosis of severe mental disorder prior to their diagnosis of heart disease | - Followed until January 1, 2007<br>- Adjusted for age, sex, and calendar period | People with SMI were significantly <u>less</u> likely to receive invasive procedures for heart disease within 5 years after their first contact (7.04% vs. 12.27% in people with and without SMI, respectively) | | | Mortality rate ratios (MRR) of myocardial infarction in patients :<br>- With mental disorder vs. people without mental disorder: 2.81 (95%CI: 2.50~3.17);<br><br>1-year mortality of heart disease after the first heart disease contact was 2.80% and 1.00% for people with or without previous psychiatric admissions respectively<br><br>Mortality of heart disease within 5 years after the first heart disease contact was 8.26% and 2.86% for people with or without previous psychiatric |

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| | | | | | | admissions respectively |
| Kisely (Kisely et al., 2009); Canada | - Total 49,428 patients admitted with ischemia heart disease identified from Population Health Research Unit in Nova Scotia<br>- 1,285 patients had diagnosis of 'psychosis' (including schizophrenia and other non-affective psychosis) | -1995~2001<br>- Mean age: 65.4 (SD 13.6)<br>- Adjusted for psychiatric diagnosis, age, gender, socioeconomic status, comorbid illness (Charlson-Deyo index score), and place of residence | Adjusted odds ratio (95%CI) of receiving:<br>Catheterization: 0.47 (0.38 ~0.58)<br>PTCA: 0.41 (0.29 ~0.59)<br>CABG: 0.35 (0.25~0.49) | | | Adjusted OR (95%CI) for:<br>- Unadjusted 28-day mortality: 1.56 (1.32~1.86)<br>- Adjusted 1-year mortality: 1.27 (1.09~1.48) |
| Bresee (Bresee et al., 2012); Canada | - A total of 2,310,391 people from the Alberta Health and Wellness databases<br>- 5,673 patients were schizophrenia and had coronary heart | | | Patients with schizophrenia and coronary artery disease were less likely to undergo coronary revascularization (6% versus 12%; Adjusted OR =0.55, 95% CI=0.49~0.61). | | |

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| | disease<br>- 318,145 were people without schizophrenia who had coronary heart disease | | | | | |
| Mitchell (Mitchell & Lawrence, 2011); Meta-analysis of studies worldwide | - A total of 825,754 individuals identified from 22 analyses | | Pooled hazard ratios of in people with any mental disorders:<br>- Overall relative risk of receiving comparable procedures: RR=0.86 (95% CI 0.80-0.92)<br>- Catheterization: RR=0.85 (0.76~0.95)<br>- PTCA: RR=0.87 (0.72~1.05)<br>- CABG: RR = 0.85(0.72-1.00) | Pooled hazard ratios of in people with schizophrenia:<br>- Overall relative risk of receiving comparable procedures: RR=0.53 (95% CI 0.44-0.64)<br>- PTCA: RR=0.50 (0.34~0.75)<br>- CABG: RR = 0.69(0.55-0.85) | | Pooled hazard ratios (95%CI) of one-year mortality for those with mental illness:<br>- RR=1.11 (1.00~1.24, P = 0.05) |
| Kurdyak (Kurdyak et al., 2012); Canada | - 69,911 people with incident AMI who were alive at hospitalization discharge from | - January 1, 2002 to December 31, 2006<br>- Mean age: 66.1(SD 14.7) and 67.7 (14.0) for patients with or without | | Adjusted odds ratios (95%CI) for<br>- cardiac procedures: 0.48 (0.40~0.56) | | Adjusted odds ratios (95%CI) for<br>- 30-day mortality: 1.56 (1.08~2.23) |

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| | multiple Ontario health administrative databases<br>- 809 had a diagnosis of schizophrenia | schizophrenia, respectively<br>- Adjusted for age, sex, rural residence, income, length of stay, frequency of primary care visits, whether subjects had any cardiologist visit in the year prior to admission for AMI, and medical comordities | | | | |

[1]Based on Mitchell et al's systematic review (Mitchell et al., 2009).

[2]* p< 0.001; ** p<0.01; *** p<0.05

[3] PTCA: Percutaneous transluminal coronary angioplasty

[4]CABG: Coronary artery bypass graft

Six studies have focused on schizophrenia and four on the broad category of affective disorder (included affective psychosis, bipolar disorder, and major depressive disorder; not specifically bipolar disorder). Compared to counterparts without mental illness, patients with schizophrenia or affective disorder had a significant 41~88% and 51~93% reduced likelihood of receiving cardiac catheterization, respectively. The likelihood of receiving revascularization were even lower in patients with schizophrenia (27~71% odds of receipt compared with the general population) and affective disorder (51~79 % odds of receipt compared with general population).

Nine studies reported outcomes of mortality or recurrence. Among these, significant excess risks of 28-day (56% increased risk)(Kisely et al., 2009), 30-day (19~56% increased risk)(Abrams et al., 2009; Kurdyak et al., 2012), or one-year mortality (12~34% increased risk)(Abrams et al., 2009; Druss et al., 2000; Kisely et al., 2009; Kisely et al., 2007; Laursen et al., 2009) were found in patients with any mental disorder. However, other studies found no difference in 30-day (Druss et al., 2000; Petersen et al., 2003) or one-year mortality (Plomondon et al., 2007). In subgroup analyses patients with schizophrenia or affective disorder had a higher one-year mortality (11~78%)(Abrams et al., 2009; Druss et al., 2001a), which was found to be reduced by adjusting for measures of cardiac care quality (Druss et al., 2001a). Additional analyses stratified by age or psychiatric outpatient or inpatient diagnosis further revealed that people with schizophrenia younger than 65 years of age (Young & Foster, 2000) and psychiatric patients identified based on outpatient codes (Abrams et al., 2009) have an increased likelihood of deaths following an AMI.

### 3.4 Conclusion

Although findings of population-based studies from Canada (Kisely et al., 2009; Kisely et al., 2007), Australia (Lawrence DM et al., 2003), or Denmark (Laursen et al., 2009) have more generalisability because of national healthcare systems, most research has either grouped mental illness into very broad categories (e.g. affective or non-affective psychoses) or has focused on schizophrenia specifically (Druss et al., 2000; Jones LE & Carney, 2005; Kisely et al., 2007; Lawrence DM et al., 2003; Petersen et al., 2003). Given the significant heterogeneity ($I$= 98.1%) reported in a meta-analysis to quantify differences of invasive coronary intervention rates in people with any mental disorder or severe mental illness (Mitchell & Lawrence, 2011), and although previous research has reported reduced likelihood of receiving invasive procedures and increased mortality rates following an AMI in people with schizophrenia, very little is known specifically about bipolar disorders in this respect. Finally, as described in the previous chapter, it should be borne in mind that only relevant studies published in English or Chinese language were included; although through a process of checking through titles and abstracts lists from Pubmed or Ovid medline, the candidate did not find any other relevant literature from East Asia.

# CHAPTER 4

# LITERATURE REVIEW OF THE ASSOCIATION BETWEEN ANTIPSYCHOTIC USE AND ACUTE MYOCARDIAL INFARCTION

## 4.1 Introduction

The risk of acute myocardial infarction (AMI) among patients with serious mental illness (SMI) has been discussed in the previous chapters. Another important question arising concerns the degree of association between antipsychotic exposure and risk of AMI. This chapter reviews studies that investigated this question and summarizes their findings.

## 4.2 Literature search

### 4.2.1 Search strategy

The main purpose was to identify research investigating associations between antipsychotic agents and myocardial infarction; therefore individual articles on Pubmed and Ovid Medline were extracted for review using the following search strings:

(antipsychotic* AND agents) AND (myocardial infarction OR coronary heart disease)
or (neuroleptic* AND agents) AND (myocardial infarction OR coronary heart disease)
or (major AND tranquiliz*) AND (myocardial infarction OR coronary heart disease)
or (psych*) AND (myocardial infarction OR coronary heart disease).

The searches were restricted to studies of human subjects over 18 years of age, and did not restrict on duration or timing of studies, or on geographical location. A search for review articles was carried out before searching for individual articles, and one systematic review was found (Brauer, 2011). Titles of articles

identified from Pubmed or Ovid Medline which were not on the reference list of the review were further examined by candidate. Abstracts of articles not written in English or Chinese language were further examined and excluded if the contents were not relevant to the objective of search. The searches were performed initially in July 2011, with the main database searches updated in August 2012. Abstracts and full text from research papers or review articles that contained any of the above keywords were assessed. References from these articles that were potentially relevant to the search topic were also accessed.

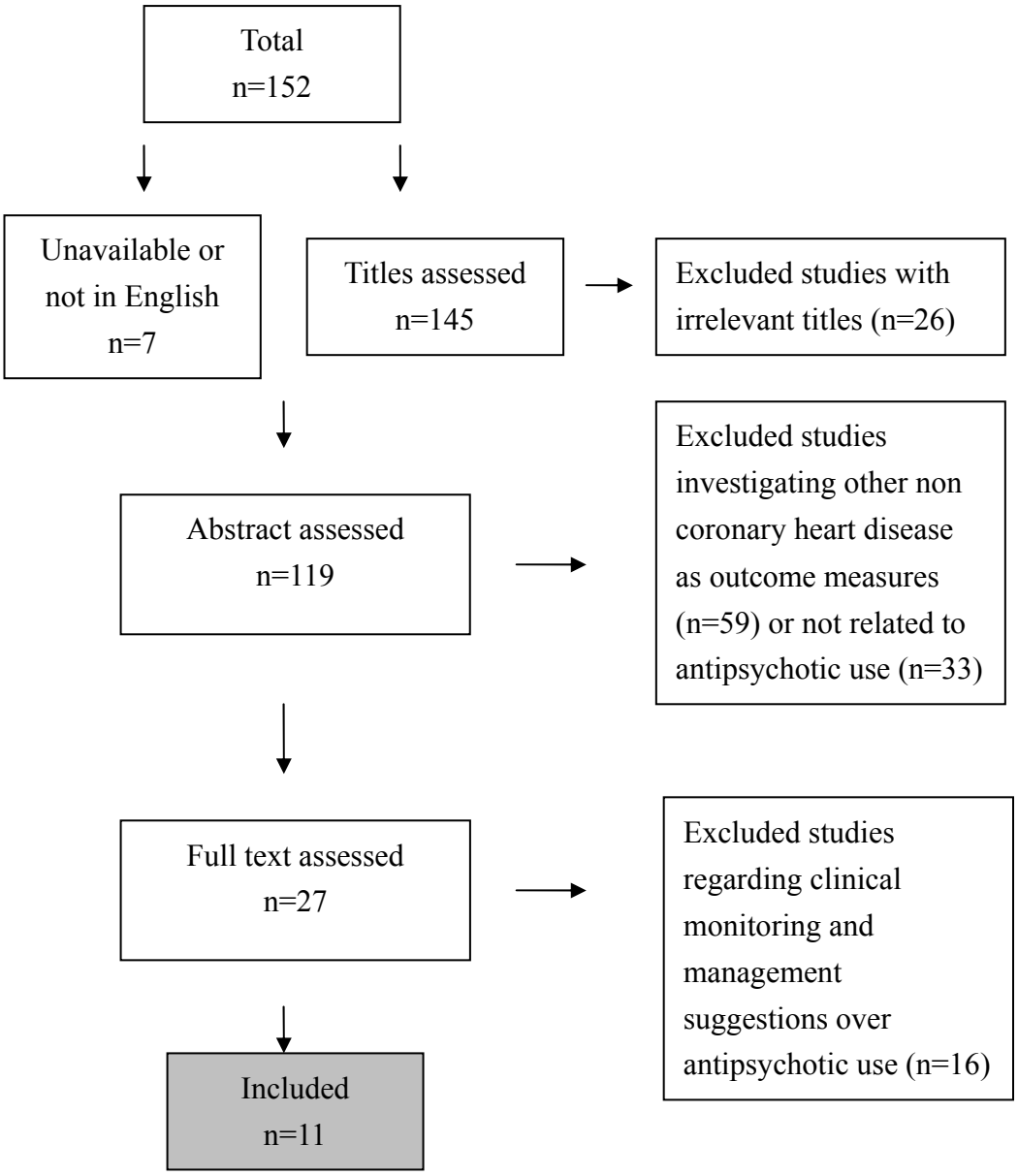
### 4.2.2 Selection of studies

Studies that reported any study population with measures of past, current or cumulative prescription instances of any antipsychotic agent and used AMI or coronary heart disease as the main outcomes of interest were included. The main outcome of interest was the association between antipsychotic agents and the incidence of AMI expressed as relative risk (RR) or hazard ratio (HR), or the association between AMI and prior antipsychotic exposure expressed in odds ratios (ORs). Both unadjuted and adjusted results were considered. Findings assessing dose–response relationships or results of sub-analyses comparing gender, age and history of cardiovascular disease strata were also reviewed.

Studies not associated with antipsychotic agent, or solely about clinical monitoring suggestions over antipsychotic use were not included. A previous review (Brauer et al., 2011) had restricted their search criteria to studies with exposures to antipsychotic or placebo or other alternative medication for at least 12 months, but since the short-term effect of antipsychotic agent was also of

interest, no restriction rules were made for the time of exposure. The systematic reduction of articles was described in **Figure 4.1**.

**Figure 4.1 Flow chart of selecting the studies**



### 4.3 Summary of search findings

Of the initial 152 articles identified, titles and abstracts were screened first, followed by full text review. There were 141 studies that were not relevant or not matching search criteria which were discarded.

Previous investigations of the association between AMI and antipsychotic exposures have used following study designs summarized briefly below:

a) 'Case control' studies have been conducted which have selected groups with or without a diagnosis of AMI and compared the odds of antipsychotic exposure.

b) Cohort studies have been reported where the outcome of developing an episode of AMI or not has been investigated among groups of people with or without the exposure to antipsychotic.

c) 'Self-controlled case series' have been conducted, comparing the relative incidence estimates of high- risk period with low- risk period from exposed cases to eliminate control-selection bias.

Results from the above designs are summarized in the following sections:

#### 4.3.1 Findings from case control studies

Three case control studies were found which compared the exposure of antipsychotic between groups with or without AMI. Among them, sources of medication records and types of medication covered were quite heterogeneous. As summarized in **Table 4.1**, the following two studies found a 1.5~6.2 times increased odds of exposures of antipsychotic or neuroleptic agents in people with AMI. Thorogood et al. specifically focused on thioxanthene and phenothiazine agents by interviewing general practitioners and using patient records (Thorogood

et al., 1992) but included only fatal AMI. One study investigated patient records for neuroleptic use among incident cases of AMI that were either hospitalized or died because of AMI (Penttinen & Valonen, 1996). However, the exposure was quite rare (4 cases of AMI vs. 6 non-AMI controls were exposed to antipsychotic). In addition, the generalisability of the above two studies might be limited because Thorogood et al. only focused on female and Penttinen et al. focused on male subjects. The study reported by Nakagawa had the largest sample size, making use of a population-based prescription database (Nakagawa et al., 2006), but only investigating first-time hospitalizations for AMI. Cumulative doses of antipsychotic were only analyzed in Nakagawa's study.

In **Table 4.1**, two case-control studies found higher frequencies of exposure to antipsychotic agents among patients with AMI, reporting ORs or RRs ranging from 1.5 to 6.2 (Penttinen & Valonen, 1996; Thorogood et al., 1992). However, the largest, with the highest internal validity reported by Nakagawa et al. found negative associations between myocardial infarction and antipsychotic exposures although not to a statistically significant extent (Nakagawa et al., 2006). These authors further reported that there were no clear trends in a dose-response analysis, indicating that the risk of AMI was not influenced by the cumulative defined daily dose prescribed to the patients. Other detailed results are summarized in **Table 4.1**.

**Table 4.1 Summarizing case control studies reporting associations between AMI and antipsychotic use**[1]

| Study, author, and country | Sample members of AMI cases and non-AMI controls | Study years; Age or mean age of inclusion | Compare the exposure to antipsychotic among Sample members | Numbers of exposure in AMI cases or non-AMI control groups | Control for confounding factors | Main findings: (with 95% confidence intervals) |
|---|---|---|---|---|---|---|
| Thorogood (Thorogood et al., 1992), UK | - Women aged 16 to 39;<br>- 161 AMI cases and 309 non-AMI controls; | - 1986 ~ 1988<br>- Not given | - Compared recent users and ever users vs. non-users of antipsychotic. | - AMI cases exposed to antipsychotic: 25;<br>- Non-AMI controls exposed to antipsychotic: 13. | - 1:2 matching by age, marital status, and general practitioner.<br>- | Relative risk (RR) for ever use of:<br>-Thioxanthene: 4.6 (0.90~ 24).<br>-Phenothiazine: 6.2 (2.0~ 19.1).<br>-Thioxanthene: 2.0 (0.3~ 14.2). |
| Penttinen (Penttinen & Valonen, 1996), Finland | - 83 AMI cases and 249 non-AMI controls among 3172 male farmers | - 1980~1992<br>- Not given | - Compared ever users vs. non-users of antipsychotic | - AMI cases exposed to antipsychotic: 4;<br>- Non-AMI controls exposed to antipsychotic: 6. | - 1:3 matching by age, smoking, social status, and country of residence. | OR for ever use of neuroleptic agents: 1.5 (0.40~ 6.00) |
| Nakagawa (Nakagawa et al., 2006), Denmark | 21,377 AMI patients matched with 106,885 non-A MI population controls | - 1992~2004<br>- Mean age: 69.4 | - Compared low, moderate, or high cumulative dose on users vs non-users of antipsychotic | - AMI cases exposed to antipsychotic: 1024;<br>- Non-AAMI controls exposed to antipsychotic: 4511. | - 1:5 matching by age, sex, and residence. | Adjusted OR of MI:<br>- For current users of atypical antipsychotic: 0.98 (0.88~1.09)<br>- For current users of typical antipsychotic: 0.99 (0.96~1.01) |

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| | | | | | | - For current users of both: 0.92 (0.71~1.20)<br>- For current female users of atypical antipsychotic: 1.02 (0.88~1.18)<br>- For current male users of atypical antipsychotic: 0.94 (0.81~1.09)<br>- For current female users of typical antipsychotic: 0.99 (0.94~1.04)<br>- For current male users of typical antipsychotic: 1.004 (0.94~1.06) |

[1]Mainly adapted from Brauer (Brauer et al., 2011)

### 4.3.2 Findings from cohort studies

Seven cohort studies were identified which reported the risk of AMI either among patients with or without antipsychotic exposure, or users with typical vs. atypical antipsychotic (summarized in **Table 4.2**).

As shown in **Table 4.2**, sources of subjects varied in these research. There were studies that focused on patients with schizophrenia (Enger *et al*., 2004; Jerrell & McIntyre, 2007; Osborn *et al*., 2007)) or other severe mental illness (Osborn *et al*., 2007); as well as studies only focusing on older people with mental disorders (Barak et al., 2007; Mehta et al., 2011; Pariente et al., 2012), including a cohort of older patients with dementia who had recently initiated acetyl cholinesterase inhibitor treatment (Pariente *et al*., 2012). Exposure status and outcome measures among these studies were quite heterogeneous. Pariente *et al*. (2012) and Enger *et al*. (2004) compared incident AMI among users and non-users of typical or atypical antipsychotic. Pratt *et al*. (1996) only focused on the risk of incident AMI among those exposed or not exposed to phenothiazine agents; while Jerrell *et al*. (2007) and Mehta *et al*. (2011) compared the risk of incident AMI or serious cardiac events (AMI included) between users of typical or atypical antipsychotic agents. Similar to Mehta, the outcome that Barak *et al*. (2007) measured was also a wide group of cardio- or cerebrovascular events that included AMI among patients with or without antipsychotic exposure. There have also been limitations of loss to follow-up in previous research; it was reported that almost half of the sample members in Pratt *et al*'s (1996) cohort either died or were lost to follow up; 40% of the sample members were also reported to have left the database before the study ended in Enger *et al*'s (2004) report.

The study reported by Osborn *et al*., (2007) was also included as relevant literature, which compared mortality due to coronary heart disease among patients with SMI with or without exposures to antipsychotic. Concerning the dose-response relationship, Enger *et al*. (2004) calculated ratios of dispensed days to total days (lowest exposure as reference) representing the intensity of dose, whereas Osborn *et al*. (2007) compared total dose of antipsychotic prescribed among different age groups of patients with SMI.

Accepting these differences in methodology, among the seven studies, an increased risk of AMI was found in people with antipsychotic use compared to those without in three historic cohort studies with odds ratios (OR) or hazard ratios (HR) ranged from 1.15 to 5.34 (Enger *et al*., 2004; Pariente *et al*., 2012; Pratt *et al*., 1996). Osborn *et al*. (2007) found that the excess risk of coronary heart disease associated with antipsychotic use in SMI ranged from 0.98 in patients older than 75 years of age, to 3.13 in patients aged between 18~49, with the greatest risk in the highest dose group. However, Enger *et al*. (2004) found an inverse dose-response relationship. Barak *et al*. (2007) and Jerrell *et al*. (2007) found no significant association between risk of AMI and antipsychotic exposures, but they either did not measure the effects of relative risks (Barak *et al*., 2007), or just compared the risk of AMI among users of typical antipsychotic versus atypical (Jerrell & McIntyre, 2007; Mehta et al., 2011).

**Table 4.2 Summarizing cohort studies reporting associations between antipsychotic use and AMI**

| Study, author, and country | Sample members | Study years; Age or mean age of inclusion | Compare the risk of AMI among the following subgroups | Number of events (AMI) in antipsychotic exposed and non-exposed groups | Control for confounding factors | Main findings: (with 95% confidence intervals) |
|---|---|---|---|---|---|---|
| Pratt (Pratt et al., 1996); US | -71 people exposed to phenothiazines and 1480 non-exposed | - 1981~1994<br>- 18~29 yrs: 36%<br>30~44 yrs: 38.2%<br>45~54 yrs: 10.2%<br>55~64 yrs: 9.4%<br>≧65 yrs: 6.2% | - Compared 'ever users' vs. non-users of antipsychotic | AMI occurred among<br>- Phenothiazine exposed patients: 8;<br>- Non-exposed: 55 | - Adjusted for age, sex, marital status, history of hypertension, and history of major depressive disorder or dysphoria | Crude Odds ratio (OR) for ever use of<br>-Phenothiazines: 3.26 (1.49~7.12);<br>-Adjusted OR for ever use of<br>-Phenothiazines: 2.92 (1.23~6.98) |
| Enger (Enger et al., 2004); US | - 1920 patients with schizophrenia matched with 9,600 people who were members that receive health care services from a large managed care organization | - 1995~1999<br>- Mean age: 38.2 | - Compared types and intensity of exposure to antipsychotics;. | AMI occurred among<br>- antipsychotic- exposed patients: 12;<br>- Non-exposed patients: 28 | - 1:5 matching by age, gender, date and health plan;<br>- Adjusted for duration of follow-up, prior diabetes, prior use of antianginal or antihypertensive medications | Adjusted relative risk (RR) of AMI:<br>- For any antipsychotic use: 4.81 (2.44~9.46)<br>- For typical antipsychotic only: 5.34 (1.75~16.30)<br>- For atypical antipsychotic only: 1.66 (0.19~14.82)<br>- For use of both types of antipsychotics: 5.22 (1.22~ |

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| | | | | | | 22.40) ;<br><br>Intensity to exposure:<br>- Medium: 0.31(0.05~1.75)<br>- Highest: 0.46 (0.13~1.69) |
| Osborn (Osborn et al., 2007);<br>UK | - 46,136 people with serious mental illness (SMI), compared with 300,426 without | - 1987~2002<br>- Median age: 46.4 for SMI group; 38.0 for control | Examined the risk of CHD mortality :<br>- Among people with or without SMI, with or without antipsychotic exposure<br>- According to terciles total dose of antipsychotic use (in chlorpromazine equivalent) among people with or without SMI | Total numbers of deaths due to coronary heart disease (CHD):<br>- In people with SMI: 618;<br>- In people without: 2293 | - Adjusted for age, sex, period, and social deprivation | Risk of CHD mortality in people with or without SMI:<br>- In SMI patients not taking antipsychotic: from 1.17 (0.94~1.46) in people older than 75 years of age, to 2.75 (1.17~6.44) in people aged between 18~49<br>- In SMI patients taking antipsychotic: from 0.98 (0.84~1.13) in people older than 75 years of age, to 3.13 (1.11~8.55) in people aged between 18~49.<br>- Risk of CHD mortality increased with total dose of antipsychotic use, especially in |

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| | | | | | | patients with SMI aged 18~49. |
| Barak (Barak et al., 2007); Isreal | - 3,111 patients admitted to an acute psychogeriatric ward in a mental health center;<br>- 2,583 patients were exposed to antipsychotic<br>- 528 patients were not exposed | - 1990~2005<br>- Mean age: 73.9 | - Compared the outcome of cardiovascular (including AMI) or cerebrovascular mortality among users of typical, atypical antipsychotic and non-users. | Cardiac (including AMI) or cerebrovascular outcomes occurred among patients exposed to:<br>- Second generation antipsychotic: 26 (out of 1,402);<br>- Conventional antipsychotic: 31(out of 1,181)<br>- No antipsychotic: 8 (out of 528) | - Did not control for confounders | Patients exposed to antipsychotic did not have more medical adverse outcomes compared to those without antipsychotic exposure:<br>- $\chi 2$ test compared cardiovascular and cerebrovascular outcomes among these three groups of typical, atypical, and no antipsychotic use yielded p values on the order of 0.29 to 0.39 |
| Jerrell (Jerrell & McIntyre, 2007); US | - 4,375 patients with schizophrenia aged 18~54 from the Medicaid<br>- Newly prescribed with typical or | - 2002~2004<br>- Mean age: 40 | - Newly prescribed users of atypical vs typical antipsychotic | Incidence of AMI and other ischemic heart diseases occurred among patients exposed to antipsychotic: 0.7% (15 out of 2231) | - Significant predictors of demographic variables and specific cerebro- or cardiovascular conditions.<br>- Age, gender, and race were not significantly | Results indicated a non-significant overall regression equation, with Likelihood ratio $\chi 2=12.06$; df=10; p=0.28.<br>With the exception of |

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|---|---|---|---|---|---|---|
| | atypical antipsychotics | | | | different across the antipsychotic groups | aripiprazole which had a lower estimate : Wald$\chi$2=7.45; p= 0.006; OR= -2.17; 0.26~ 0.80 compared to both conventional medications (haloperidol and fluphenazine). |
| Mehta (Mehta et al., 2011); US | - 39,587 Older adults (>= 50 years of age) newly prescribed with atypical (12,296) or typical (26,991) antipsychotics | - 2000~2007<br>- Mean age of 69.8 for atypical users; 69.4 for typical users after matching. | - Users of typical vs. atypical antipsychotic | Serious cardiac events (including AMI, after matching by propensity score) occurred among patients exposed to:<br>- Atypical antipsychotic: 11.9% (out of 5,580);<br>- Typical antipsychotic: 12.4% (out of 5,580) | - Matched by propensity scores calculated on the basis of more than 60 covariates<br>- These covariates were shown to be associated with the assignment of treatments with typical or atypical antipsychotic | Hazard ratios for serious cardiovascular events among patients exposed to :<br>- Atypical antipsychotic: 1.00 (reference)<br>- Typical antipsychotic: 1.21 (1.03~1.40) |
| Pariente (Pariente et al., 2012); Canada | - 37,138 Community-dwelling older patients who initiated cholinesterase inhibitor treatment (with dementia) | - 2000~2009<br>- After matching by propensity scores: Unexposed vs. exposed subcohort: 66~74 yrs: 17.9 vs. 22.3 % | - Compared users vs. non-users of antipsychotic | Incident AMI occurred among patients (after matching by propensity scores):<br>- Exposed to antipsychotic: 138 (out of 10,969)<br>Not exposed to | - Adjusted for sex, age, dementia severity, markers of potential comorbidities, and known or suspected risk farctors for AMI<br>- Matched by propensity | Hazard ratios for AMI after initiation of :<br>- Antipsychotic treatment: 2.19 (1.11~4.32) for the first 30 days<br>- 1.62 (0.99-2.65) for the first 60 days, |

| | | | | | | |
|---|---|---|---|---|---|---|
| | - Incident antipsychotic users (exposed group) vs. non-users (non-exposed group) | 75~79 yrs: 25.8 vs. 27.6 %<br>80~84 yrs: 29.3 vs. 27.3%<br>≧85 yrs: 27.0 vs. 22.8 % | | antipsychotic: 126 (out of 10,969) | scores | - 1.36 (0.89-2.08) for the first 90 days,<br>- 1.15 (0.89-1.47) for the first 365 days. |

### 4.3.3 Findings from self-controlled case series

One self-controlled case series reported by Pariente et al. was embedded in the aforementioned historic cohort of randomly-selected community-dwelling patients aged over 66 years with dementia, who were new users of cholinesterase inhibitors (Pariente et al., 2012). In this study design, all antipsychotic users with incident AMI during the follow up period were included. The number of outcome events (i.e. AMI) occurring during the time periods after the initiation of antipsychotic were compared to that during the reference periods when no antipsychotic was prescribed (periods before the initiation and after the termination of antipsychotic, see **Figure 4.2** for the illustration of Pariente's design). From the total 37,138 patients with dementia, 804 new antipsychotic users with incident AMI were selected. Incident AMI occurring in acute (1~30 days), intermediate (31~60 days), and prolonged (61~90 days) periods after the initiation of antipsychotic were quantified and compared to that occurring in the reference periods. The authors also defined and compared AMI events occurring in the remaining exposure period, defined as day 91 until the end of the last antipsychotic dispensing; and the residual risk period (withdrawal), which covered the 90 days after the end date of the last antipsychotic dispensing.

Their results showed a positive association with antipsychotic exposure: the highest incident ratios for AMI were reported in the acute period (1.78, 95% CI:1.26~2.52), followed by that in the intermediate period (1.67, 95% CI:1.09~2.56), prolonged period (1.37, 95% CI:0.82~2.28), the remaining exposure period (1.18, 95% CI:0.92~1.51), and the withdrawal period (0.80, 95% CI:0.62~1.04). Detailed information regarding numbers of AMI cases and confounders were summarized in **Table 4.3**.

**Figure 4.2 Risk periods for self-controlled case series study.**

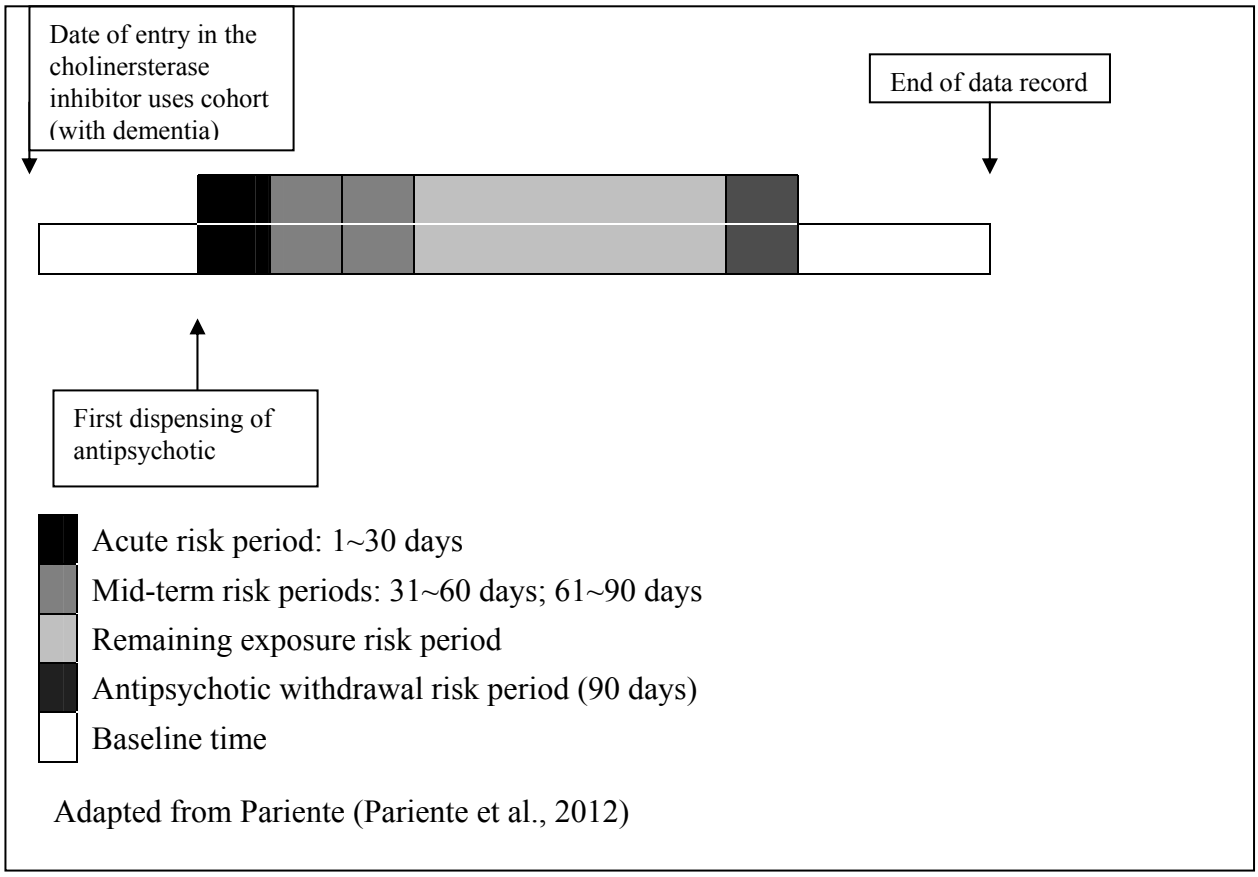


**Table 4.3 Summarizing self-control case series on the association between myocardial and antipsychotic use**

| Study, author, and country | Sample members | Study years; Design | Number of AMI cases in different periods | Control for confounding factors | Main findings: (with 95% confidence intervals) |
|---|---|---|---|---|---|
| Pariente (Pariente et al., 2012); Canada | - 804 new antipsychotic users with incident AMI during the entire follow up period were selected among 37,138 community-dwelling older patients who initiated cholinesterase inhibitor treatment (with dementia) | - 2000~2009<br>- Compare the incidence of AMI in acute (days 1-30 after the first antipsychotic dispensing), intermediate (days 31-60), or prolonged (days 61-90) period vs. reference period.<br>- The remaining exposure period was defined as day 91 until the end of the last AP dispensing.<br>- The residual risk period (withdrawal) covered the 90 days after the end date of the last AP dispensing | - Day 1~30: 31 (out of 804)<br>- Day 31~60: 21 (out of 804)<br>- Day 61~90: 16 (out of 804)<br>- Remaining exposure period: 198 (out of 804)<br>- Withdrawal period: 68 (out of 804)<br>- Unexposed period: 470 (out of 804) (refence group) | - Intra-individual comparisons<br>- Adjusted for age at the first AMI to account for the aging of the cohort.<br>- By partitioning the observation time in 5 age groups. | Incident ratios for MI :<br>- Day 1~30: 1.78 (1.26~2.52)<br>- Day 31~60: 1.67 (1.09~2.56)<br>- Day 61~90: 1.37 (0.82~2.28)<br>- Remaining exposure period: 1.18 (0.92~1.51)<br>- Withdrawal period: 0.80 (0.62~1.04) |

## 4.4 Conclusion

Inconclusive results have been reported from the research to date on the association between risk of myocardial infarction and antipsychotic use. Some studies have found a moderate to strong increase in the risk of AMI among users of typical antipsychotic agents; weak associations or no association have been found for atypical antipsychotic use as an exposure. Although the case-control study with the largest sample size (Nakagawa *et al*. 2006) found no association between exposure to any type of antipsychotic agent and myocardial infarction within the general population, a recent large cohort study (Pariente *et al*. 2011) reported increased risk of AMI in new users of antipsychotic among patients with dementia compared with non-users. Such increased risk seemed to be the highest during the first month of antipsychotic prescription. Most studies to date, however, have tended to investigate antipsychotic use in general population samples or older adults rather than use specifically in people with schizophrenia or bipolar disorder who may have particular dosing profiles that do not generalize. In addition, most studies regarding antipsychotic exposure and risks of AMI have focused on relatively long-duration exposures or follow-up periods and are not equipped to detect short-term effects. Furthermore, observational studies cannot exclude residual confounding arising from different characteristics of people receiving or not receiving antipsychotics while randomized control trials tend to focus on relatively healthy samples in relatively controlled clinical settings with insufficient statistical power, even when combined, to detect an adverse outcome such as AMI.

# CHAPTER 5

# REMAINING AREAS OF UNCERTAINTY IN THE LITERATURE, PRINCIPAL OBJECTIVES, AND STUDY HYPOTHESES

### 5.1 Remaining areas of uncertainty

Previous research investigating the risk of acute myocardial infarction (AMI), receipt of invasive coronary intervention and outcomes following AMI, and associations of AMI and antipsychotic use in people with serious mental illness (SMI) have been summarized in **Chapters 2~4**. Principally, studies in this field focusing specifically on AMI in people with SMI are relatively scant, espeically those which have defined subgroups of schizophrenia or bipolar disorder. This is likely to be due to methodological challenges since the prevalence of SMI and AMI comorbidity are relatively low.

The background literature was concluded to be weak in the following areas:

a) There were reasonable amount of literature comparing the risk of AMI in patients with and without schizophrenia, but relatively little comparing this outcome in people with or without bipolar disorder.
b) Previous comparisons of AMI risk between people with and without SMI have used samples with broad age ranges. Little is known about modifying effects of age and gender on this association.
c) The majority of analyses of invasive coronary intervention receipt have relied on data from health systems with incomplete and selected coverage, such as the US Medicaid and Veterans Health Administration systems. Alternatively they have been confined to specific clinical units or primary care registers.
d) It is not clear whether any elevated risk of AMI is associated with use of antipsychotic agents in people with schizophrenia or bipolar disorder.
e) Research to date has been conducted in Western or developed countries, with little or no evidence from East Asian countries. Results regarding the receipts of invasive coronary interventions in people with SMI might, in particular, vary geographically because of differences in health service structures.

To address the gaps from previous literature described above, the project was designed to use the specific resource of a nationwide database: the National Health Insurance Research Database (NHIRD), which contains in-depth anonymised data on diagnoses and units of healthcare (including medication receipt) for all citizens in Taiwan. This study selected more than 300,000 enrollees from the NHIRD with and without SMI chosen at random from the 1996 to 2007. Principal objectives and primary hypotheses are stated in the following sections.

## 5.2 Study objectives

As described in previous chapters of literature review, the overall objectives for this thesis were to study further the remaining areas of uncertainty. Therefore, the study objectives included:

1. To investigate the relative risk of AMI in adult patients with SMI in Taiwan
2. To compare the receipts of invasive coronary intervention, outcomes of inpatient mortality, or recurrence of cardiovascular diseases following the first AMI among patients with or without SMI
3. To investigate the associations between AMI and recent antipsychotic exposure among people with SMI

## 5.3 Study hypotheses related to objectives of this thesis

### 5.3.1 To investigate the relative risk of acute myocardial infarction in adult patients with serious mental illness in Taiwan

The hypothesis was as follows:

(1) Compared with the national population, people with SMI will have a higher risk of AMI, independent of age, sex, previous history of cardiovascular risk factors, and levels of monthly income and urbanization levels.

### 5.3.2 To compare the receipts of invasive coronary interventions, outcomes of inpatient mortality, or recurrence of cardiovascular diseases following the first acute myocardial infarction among patients with or without serious mental illness

Comparing receipts of invasive coronary interventions and outcomes following AMI between people with a previous history of SMI (cases) and those without such a history (controls), the hypotheses were as follows:

(1) Diagnostic catheterization will be lower in cases compared to controls.

(2) Receipt of revascularization will be lower in cases compared to controls.

(3) Receipt of revascularization after catheterization will be lower in cases compared to controls.

(4) Inpatient complications following AMI will be higher in cases compared to controls.

(5) The 30-day inpatient mortality following an AMI will be higher in cases compared to controls.

(6) Recurrence of AMI within and after one year after discharge of index AMI episode will be higher in cases compared to controls.

(7) Hospitalizations due to other cardiovascular diseases within and after one year after discharge of index AMI episode will be higher in cases compared to controls.

### 5.3.3 To investigate the associations between acute myocardial infarction and recent antipsychotic exposure among people with serious mental illness

Comparing a more recent (case) with a more distant (control) time period in people with SMI who experienced an AMI, the hypotheses were as follows:

(1) Antipsychotic exposure will be more common in the case time period compared

to the control time period.

(2) The average dose of antipsychotic will be higher in the case period compared to the control period.

(3) Use of typical antipsychotic will be more common in the case period compared to the control period (the rationale being that a short-term relationship would potentially act via conduction deficits associated with typical agents rather than the cardiometabolic effects associated with atypical agents).

# CHAPTER 6

# CORE MATERIALS AND METHODS

## 6.1 Introduction and chapter plan

In this study, a series of secondary analyses were carried out using historic cohorts derived from a nationwide database in order to test the study hypotheses. This chapter describes the details of the population-based datasets used, from the application to the assembly of the datasets, the principal data management processes, and the generation of variables relevant to the analyses presented in the subsequent three results chapters (**Chapters 7~9**). The overall protocol for ascertaining case and comparison groups, treatment receipts following acute myocardial infarction (AMI), and ascertainment of antipsychotic and cardiovascular medication use will be described in this chapter. Specific variables or covariates relevant to individual hypothesis and statistical approaches will be described in detail within each of the results chapters.

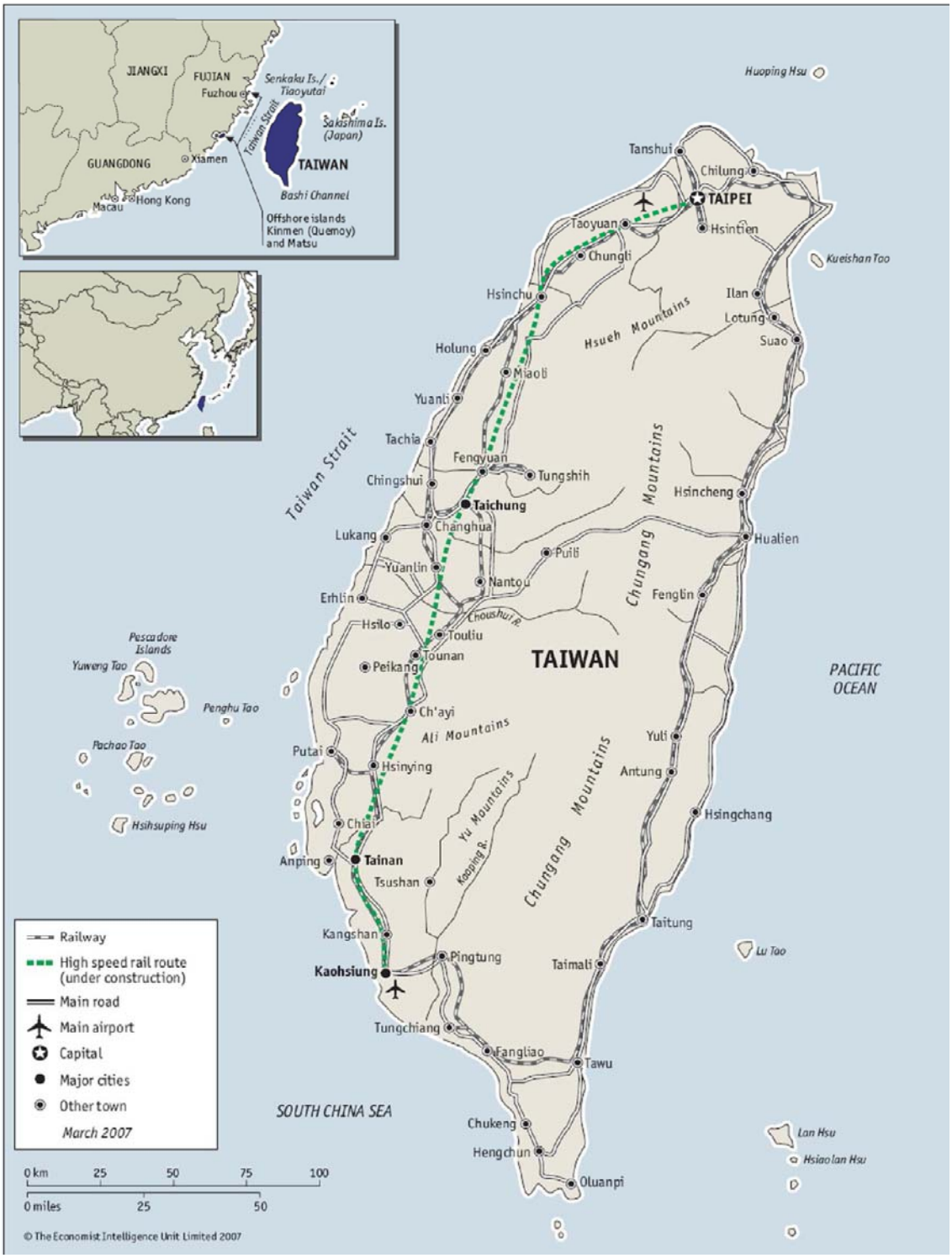
## 6.2 Data source

### 6.2.1 Relevant background information regarding health service provision in Taiwan

Taiwan, an island of 36,000 square kilometers situated on the southeast of China, (see **Figure 6.1**), has a population of approximately twenty three million people in 2001. The health care system in Taiwan currently offers nearly 1.6 physicians and 5.9 hospital beds per 1,000 population (Taiwan country profile, 2005). The per capita health expenditure was around US$951 in year 2009. The overall health expenditure constitutes 6~7 percent of the gross domestic product (GDP)(World Economic Outlook Database-April 2010). The overall life expectancy in 2009 was 78 years (Taiwan country profile, 2005). The providers (hospitals or clinics) are accredited into four main categories of medical centers, regional hospitals, district hospitals, and others (mostly solo-practice clinics) by the Department of Health of the Executive Yuan according to their numbers of beds and staff, service provisions, and quality of

care. Patients with psychiatric disorders mostly received psychiatric or medical services from above the level of district hospitals.

**Figure 6.1 Map of Taiwan**




(Source: Country Profile of Taiwan, The Economist Intelligence Unit, 2007)

### 6.2.2 Setting: the National Health Insurance (NHI) system in Taiwan

In order to provide people in Taiwan with equal access to medical care without financial burden, a single-payer medical insurance program, the National Health Insurance (NHI) system, was launched on March 1, 1995. All residents in Taiwan (except for military personnel and prisoners, whose medical expenses are paid by the government when needed) were required by law to join the NHI program, and by 2001, over 99% of residents (about 22.8 million out of the total population of 23 million) were included. The NHI system provides near-universal coverage of health care (comparable to the NHS model in the UK) including hospitalization, ambulatory care, and drugs with low fixed co-payment rate (US $5 per visit). With official registration, patients with severe mental or physical illness can be exempted from such co-payments. Under the NHI system, people in Taiwan have the option to access any hospital or physician at any time without maximum limits on attendances, nor is there the restricting requirement of visiting a gate keeper practitioner first.

Each resident's insurance premium is calculated on the basis of the 'Insured Amount', which takes individual or household income into account. The insured person, employer, and government have to share 35% to 100% of the premium, depending on the characteristics of their employer (eg. employers from private companies have to share 35% of their employees' insurance premiums, whereas the government has to pay for 60~70% of their own employees' premiums). People who are unemployed will either be insured as a family dependent or be registered with the social welfare system to receive benefits. People with disability or from lower income families, would receive 100% public subsidies from the government.

Every enrollee needs to insert the Health IC smart card into the electronic card reader every time they see the doctor. The Health IC smart card is a credit-card-size card

that contains the photo of the holder and a 32 kilobytes chip that provides the enrollee's profile (Name, ID number, and date of birth) for identification purposes (see **Figure 6.2**).

**Figure 6.2 The Health Smart IC card of the National Health System**


Every time physicians see a patient, they need to type the codes for diagnoses, as well as all medications, invasive procedures, and dates of inpatient care, into the computer (NHIRD, 2006). The medical service providers (hospital or clinic authorities) collect these information and upload the medical bills via internet to the Bureau of National Health Insurance every 24 hours to claim money for relevant treatments or procedures. The Bureau of National Health Insurance requests the above information to be coded using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). This is a classification system consists of disease coding numbers, as well as surgical, diagnostic, and therapeutic procedures listed in tabular forms; and is based on the World Health Organization's Ninth Revision, International Classification of Diseases (ICD-9) (WHO, 2011).

### 6.2.3 The Taiwan National Health Insurance Research Database (NHIRD)

The source of data for this thesis was a nationwide database, the Taiwan National Health Insurance Research Database (NHIRD), derived from the National Health Insurance (NHI) system in Taiwan for research purposes. The NHIRD includes records of all medical services and individual interventions received at an individual level, including ambulatory (outpatient and primary) care, hospitalization, emergency care, and drug prescriptions. Every year, the National Health Insurance Research Institute collects the information on service use from the Bureau of National Health Insurance, scrambles and de-identifies the data to form the original files of NHIRD.

The NHIRD is in turn organized into different subsets, the following of which were used in the analyses presented here and are described in detail below-- the *Psychiatric Inpatients Medical Claim Dataset* (PIMC) and the *Longitudinal Health Insurance Research Database 2000* (LHIRD2000).

#### 6.2.3.1 The *Psychiatric Inpatients Medical Claim Dataset* (PIMC)

The *Psychiatric Inpatients Medical Claim* Dataset (PIMC) contains claim-related data on visits to hospitals (registry, ambulatory care, admissions, and drug use subsets) by all people in Taiwan who had ever been hospitalized within a psychiatric department between the years 1996 to 2001, regardless of any physical healthcare received. While this provides a large sample of people with relatively rare mental disorders, an important consideration is that people with mental disorders who have only attended as outpatients during the period of interest are not included in the PIMC.

#### 6.2.3.2 The *Longitudinal Health Insurance Research Database 2000*

**(LHIRD2000)**

The *Longitudinal Health Insurance Research Database 2000* (LHIRD2000) comprises original claim-related data (registry, ambulatory care, admissions, and drug use subsets) from the year 1996 to 2007 of 1 million individuals selected randomly from the 21 million total enrollees in the Taiwan NHI program in the year 2000 (NHIRD, 2008). Of relevance to the study described in this thesis, someone who is completely healthy and not requiring medical review would still be eligible for random selection, as would people with mental disorders receiving outpatient care. The methodology of the random selection is described in detail on the NHIRD website (http://www.nhir.org.tw/nhird//date_cohort.htm) (NHIRD, 2009). No significant differences in age or gender distribution have been found between LHIRD2000, the NHIRD, and the known population distributions in Taiwan derived from census data (NHIRD, 2006). Records of medical service use of these selected people from 1996 to 2007 were available for analysis.

## 6.3 Samples

### 6.3.1 Inclusion criteria for the 'case' cohort

1. People registered on either or both of the PIMC and LHIRD2000 datasets.
2. Aged 18 and above at baseline (01.01.1996).
3. All people who had ever been given a diagnosis of schizophrenia (ICD-9-CM 295.XX) and bipolar disorders (ICD-9-CM 296.XX, other than major depressive disorder, ICD-9-CM 296.2X~296.3X) from the year 1996 to 2007 were selected as the 'study' cohort. The ICD-9-CM codes for psychiatric diagnoses included or excluded in the case cohort were listed out in **Table 6.1**.

**Table 6.1 Main ICD-9-CM codes for psychiatric diagnoses used in this thesis**

| ICD-9-CM codes | Diagnosis |
|---|---|
| Inclusion diagnoses of the study cohort | |
| 295.XX | Schizophrenia |
| (including 295.7X) | Schizoaffective disorder |
| 296.XX | Affective psychoses |
| (including 296.4X) | Bipolar affective disorder |
| (other than 296.2X~296.3X) | Major depressive disorder |
| Exclusion diagnoses of the study and comparison cohort | |
| 294.XX | Organic psychotic condition |
| (including 294.1X) | Dementia |
| 297.XX | Paranoid state |

#### 6.3.1.1 Hierarchical algorithm of psychiatric diagnoses ('case' cohort)

If people were found to have received diagnoses of schizophrenia and bipolar disorder, schizophrenia and organic mental disorder, or bipolar disorder and organic mental disorder during the follow up period, the main psychiatric diagnoses were then assigned by hierarchical algorithm (organic mental disorder > schizophrenia > bipolar disorder), in which an individual would be diagnosed with schizophrenia if he had received the diagnosis of schizophrenia during the 12- year period and had not received a diagnosis of organic mental disorder.

The diagnosis of bipolar disorder would only be assigned if an individual had never received the diagnoses of schizophrenia, schizoaffective disorder, paranoid state, or organic mental disorder. People on the LHID2000 but not the PIMC who had been diagnosed with schizophrenia or bipolar disorder (i.e. who had only been seen as outpatients) between 1996 and 2007 were also included, this group being too small to analyze separately (as described later).

Individuals with schizophrenia or bipolar disorder being identified from the above criteria are called the 'case cohort'; and people from the rest of the population are called the 'comparison cohort' throughout this thesis. However, in **Chapter 9,** where a 'case-crossover design' is utilized, different nomenclatures of the 'case period' (indicating the time period proximal to index AMI episode) or the 'control period' (or the time period distal to index AMI episode) are applied.

### 6.3.2 Inclusion criteria for the comparison cohort

1. People registered on the LHIRD2000 dataset.
2. Aged 18 and above at baseline (01.01.1996)

### 6.3.3 Exclusion criteria for the comparison cohort

1. All people who had received a diagnosis of organic mental disorder (ICD-9-CM 294.XX), and paranoid state (ICD-9-CM 297.XX) from the year 1996 to 2007.
2. People who had received a diagnosis of schizophrenia or schizoaffective disorder (ICD-9-CM 295.XX) or bipolar disorders (ICD-9-CM 296.XX) from the year 1996 to 2007 were excluded from the comparison cohort and re-classified to the case cohort, as were those who overlapped on both the PIMC and the LHID2000 datasets

## 6.4 Ascertainment of acute myocardial infarction

First diagnosis of AMI (ICD-9-CM 410.XX) from claim data of ambulatory care, emergency services, and hospitalization during 1996 to 2007, was defined and is referred to as the index AMI episode for brevity's sake. An important consideration for the study described in this thesis was that the index AMI was the first AMI episode within the specified period and that no data were available for the period before 1996.

### 6.5 Independent variables

The rationale for investigating the study hypotheses is summarized in previous chapters. As described in **Chapter 1**, the following factors are widely recognised to be associated with increased risk of AMI and worse outcomes after AMI: diabetes mellitus, hypertension, hyperlipidaemia, male gender, tobacco use, family history of atherosclerotic arterial disease, low socioeconomic status, stress, and negative emotions (Cotran RS, 1994; Druss & Rosenheck, 2000; Druss et al., 2002; Lin et al., 2006; Nyboe et al., 1989). As has also been summarised earlier, most of these risk factors are recognised to occur more commonly in people with SMI (Robson & Gray, 2007) than those without. Variables used in all analyses are described here and other analysis-specific covariates are described later within each separate result chapter. **Table 6.2** summarized the following measurements extracted from the dataset by the candidate:

1. Demographic characteristics:

(a) Age at study entry: Age at study entry was calculated from the difference between the date of study entry and the date of birth. For the case cohort, the date of study entry was defined as the date of the first diagnosis of schizophrenia or bipolar disorder in the dataset; for the comparison cohort, it was defined as the date of first medical contact on the dataset (both pertaining to a study period from 1996 to 2007). Age at study entry was also categorised into five groups based on its distribution (as shown in **Table 6.2**) and was entered in the main analyses as appropriate in both continuous and categorical format.

**Table 6.2 Summary of variables used in the study**

| Variables | Characteristics | Measures |
|---|---|---|
| Age at study entry<br>*Mean age at study entry was also calculated as a continuous variable | 5 groups based on its distribution | 1= 18-34<br>2= 35-44<br>3= 45-54<br>4= 55-64<br>5= 65 and above |
| Age at first AMI<br>*Mean age at study entry was also calculated as a continuous variable | 5 groups based on its distribution | 1= 18-34<br>2= 35-44<br>3= 45-54<br>4= 55-64<br>5= 65 and above |
| Gender | 2 groups | 0= Female<br>1= Male |
| Levels of monthly income | 4 groups based on previous literature (Lin et al., 2010a) | 0= NT$ 0<br>1= NT$ 1~15840 (≤USD 528)<br>2= NT$ 15841 ~ 25000 (USD 528~833)<br>3= ≧NT$ 25001 (≧ USD 834) |
| Levels of urbanization of residence | 5 groups based on locations and population statistics (see following text for explanation) | 1= most urbanized<br>2<br>3<br>4<br>5= least urbanized |
| Schizophrenia | 2 groups based on having this diagnosis or not | 0 = ‘No’<br>1 = ‘Yes’ |
| Bipolar disorder | 2 groups based on having this diagnosis or not | 0 = ‘No’<br>1 = ‘Yes’ |
| History of ischemic or | 2 groups per each type | 0 = ‘No’ |

| | | |
|---|---|---|
| coronary heart disease (two different variables: one type is if the diagnosis was identified before study entry for analysis in **Chapter 7**; another type is if the diagnosis was identified before index AMI for analysis in **Chapters 8 and 9**). | based on having such history or not (please refer to **Table 6.1**) | 1 = 'Yes' |
| History of hypertension (two different variables: one type is if the diagnosis was identified before study entry for analysis in **Chapter 7**; another type is if the diagnosis was identified before index AMI for analysis in **Chapters 8 and 9**). | 2 groups based on having such history or not | 0 = 'No'<br>1 = 'Yes' |
| History of diabetes (two different variables: one type is if the diagnosis was identified before study entry for analysis in **Chapter 7**; another type is if the diagnosis was identified before index AMI for analysis in **Chapters 8 and 9**). | 2 groups based on having such history or not | 0 = 'No'<br>1 = 'Yes' |
| History of hyperlipidemia (two different variables: one type is if the diagnosis was identified before study entry for analysis in **Chapter 7**; another type is if the diagnosis was identified before index AMI for analysis in **Chapters 8 and 9**). | 2 groups based on having such history or not | 0 = 'No'<br>1 = 'Yes' |

| | | |
|---|---|---|
| History of alcohol use disorders<br>(two different variables: one type is if the diagnosis was identified before study entry for analysis in **Chapter 7**; another type is if the diagnosis was identified before index AMI for analysis in **Chapters 8 and 9**). | 2 groups based on having such history or not | 0 = 'No'<br>1 = 'Yes' |
| Acute myocardial infarction | 2 groups based on having the episode or not | 0 = 'No'<br>1 = 'Yes' |
| History of visiting psychiatric department before study entry | 2 groups based on having the episode or not | 0 = 'No'<br>1 = 'Yes' |
| Levels of hospital patient visits before study entry | 4 groups based on the levels of hospital | 1 = Medical center<br>2 = Regional hospital<br>3 = District hospital<br>4 = Others |
| Levels of hospital of which the first AMI episode was diagnosed | 4 groups based on the levels of hospital | 1 = Medical center<br>2 = Regional hospital<br>3 = District hospital<br>4 = Others |
| Levels of urbanization in hospitals of which the first AMI was diagnosed | 5 groups based on the locations | 1= most urbanized<br>2<br>3<br>4<br>5= least urbanized |
| Hospital teaching status | 2 groups | 0 = 'No'<br>1 = 'Yes' |
| Status of receiving particular intervention following AMI, or antipsychotic before AMI, | 2 groups for each variable appeared in different result chapters of this thesis | 0 = 'No'<br>1 = 'Yes' |

| | | |
|---|---|---|
| or antidepressant before AMI, or cardiovascular medications before AMI | | |
| Dates of the conditions listed on the right | | • Registration to the National Health Insurance<br>• First visit identified in the database<br>• First diagnosis of psychiatric disorders<br>• First diagnosis of AMI<br>• First diagnosis of cardiovascular risk factors<br>• Death during hospitalization or loss follow up (withdrawal from NHI register) during the study period (also refer to the methodology in Chapter 7)<br>• Prescriptions of antipsychotic, antidepressants, or cardiovascular drugs in ambulatory visit or hospitalization. |

(b) Age at index AMI: Age at index AMI is defined as the difference between the date of the index AMI (definition described above) and the date of birth. Similar to age of study entry, age of first AMI was also categorised into 5 groups based on its distribution. Reasons for adjusting age at index AMI are that the incidence of AMI increases with age. Studies have shown among patients hospitalized due to AMI, over one third aged over 70 (McMechan & Adgey, 1998; Rask-Madsen et al., 1997). In addition, 80% of mortality in AMI occurs in people aged over 65; 60% in people aged over 75 (Gurwitz et al., 1992).

(c) Gender: Gender is categorized into 2 groups. The reason for adjusting gender is that the prevalence of AMI is higher in men (Wilson et al., 1998).

(d) Levels of income: The 'Insured amount' record applied to the individual beneficiary (or to the household in the case of unemployment or a lower income family) from the NHIRD was extracted as a proxy measure of individual and/or household income. Level of income was categorized into 4 groups according to its distribution (as shown in **Table 6.2**) and was entered into main analyses as a categorical variable. Reasons of adjusting levels of income are that not only do people with low income were found to have elevated risk of AMI, income level may also reflect the influences of education levels (Nyboe et al., 1989).

(e) Urbanization levels of residence: For the purpose of describing socioeconomic status, the urbanization levels of the 'Insured person's Area of Residence' was used as another proxy measure. The record of the 'Insured person's Area of Residence' was extracted from the NHIRD. These 'Area of Residence' measures were further stratified into 5 different levels of urbanization (as shown in **Table 6.2**) characterized using variables of population density (people per square kilometers), population ratio of people with education levels of college or above,

population ratio of people aged 65 or above, population ratio of agricultural workers, and numbers of physicians per 100,000 people based on the 2000 Taiwan census data, data of Survey of Health Maintenance Organizations' current status, and Health Service Utilization (conducted by Department of Health, Executive Yuan, R.O.C.) (Liu et al., 2006).

2. Mental disorder diagnosis: Recorded diagnoses of schizophrenia and bipolar disorder (mutually exclusive, as defined in **section 6.3.1**) were extracted as binary variables.

3.Diagnoses of cardiovascular risk factors occurring at any point during pre-defined periods. The definitions of time periods were different throughout **Chapters 7~9**. In **Chapter 7**, these diagnoses were identified as covariates if they occurred prior to study entry in case or comparison groups. In **Chapters 8 and 9**, these diagnoses were identified as covariates if they occurred prior to index AMI. These covariates were collated and coded as present/absent binary variables having extracted the data of diagnoses from ambulatory, admission, and emergency services used (also refer to **Table 6.3** for ICD-9-CM codes):

(a) Hypertension: People with hypertension carry a six- to nine- fold risk of developing coronary heart disease (Kannel, 1975). In addition, increased short- and long- term mortality of AMI were observed in people with hypertension compared to those without (Dunn, 1983; Kuller et al., 1973).

(b) Diabetes: Patients with diabetes have twice the risk of developing AMI compared to the general population (Buse et al., 2007), and having glucose intolerance is associated with a 1.5 to 2 times increase in the likelihood of developing IHD (Fuller et al., 1980).

(b) Hyperlipidaemia: The risk of ischemic heart disease is doubled when the total cholesterol to high-density lipoprotein (HDL) ratio reaches 10:1. A meta-analysis from seventeen case-control studies among patients with

cardiovascular disease also reported an increased relative risk of triglycerides from 1.1 to 1.4 times after controlling for HDL (Hokanson & Austin, 1996).

(c) Alcohol use disorders (including alcohol abuse and alcohol dependence): ICD-9-CM diagnoses of alcohol use disorders were used as a proxy measure for heavy drinking. The reason for adjusting for alcohol use disorder is that although an inverse association of cardiovascular mortality has been found with light drinking, a U-shape or J-shape curve are often used to report the relationship between the amount of alcohol consumption and all-cause mortality, indicating that excessive drinking is still associated with increased mortality (Di Castelnuovo et al., 2006; Gaziano et al., 2000).

4. Previous diagnoses indicating ischemic or coronary heart disease were ascertained within pre-defined periods and a single binary variable was defined according to the presence of any of the following diagnoses from datasets containing ambulatory, admission, and emergency services used (also see **Table 6.3**):

(a) Ischemic heart disease

(b) Angina pectoris

(c) Chronic ischemic heart disease or coronary atherosclerosis.

**Table 6.3 ICD-9-CM codes for diagnoses of cardiovascular diseases or risk factors**

| ICD-9-CM codes | Diagnosis |
|---|---|
| Diagnoses of cardiovascular diseases or risk factors | |
| 410.XX | Acute myocardial infarction |
| 401.XX | Essential hypertension |
| 250.XX | Diabetes mellitus |
| 272.XX | Disorders of lipid metabolism |
| 431.XX~434.XX | Cerebrovascular diseases (including intracranial hemorrhage, cerebral occlusions, stenosis, or thrombosis) |
| Diagnoses for coronary/ ischemic heart disease | |
| 411.XX | Other forms of ischemic heart disease |
| 412 | Old myocardial infarction |
| 413.XX | Angina pectoris |
| 414.XX | Other forms of chronic ischemic heart disease |
| Having any of the following 3 diagnoses were identified as having alcohol use disorder | |
| 291.XX | Alcoholic psychoses |
| 303.XX | Alcohol dependence syndrome |
| 305.0X | Alcohol abuse |

5. Using methods and definitions from previous research (Lin et al., 2006), the following characteristics of the hospital where the patient first received the diagnosis of AMI were classified and considered as potential confounding factors:

(a) Hospital level: This information was collected by merging the records of medical services in the study datasets described above with the registration file of hospitals containing information on their levels. All hospitals in Taiwan are classified into four different levels as follows based on their bed numbers and capability of providing clinical services:

- Medical centers are hospitals that have more than 500 beds, have responsibilities to provide medical services for severe or complex diseases, and have the capability for teaching, training, and undertaking research.
- Regional hospitals are hospitals that have more than 250 beds.
- District hospitals are those that have more than 20 beds.
- 'Other' health care providers include solo-practice clinics (0 or less than 20 beds), or government health centers located in remote areas.

(b) Levels of urbanization in the geographical location of these hospitals: Research showed that this may in particular affect the quality of care provision (Lin et al., 2006) and therefore was considered as a potential confounder. This information was collected by merging the records of medical services in the study datasets with the registration file of hospitals that contained area codes indicating their geographical locations. Similar to the methods of defining the aforementioned variable of 'urbanization levels of residence', the urbanization level of hospital was characterized into 5 levels according to the population statistics (Liu et al., 2006) of the hospital's geographical location and was used as a categorical variable in the main analysis.

(c) Whether a hospital was accredited as a teaching hospital or not (Lin et al., 2006): This status was coded as a binary variable.

### 6.6 Outcome variables for intervention receipts of AMI

Records of the following post-AMI procedures (also refer to **Table 6.4** for ICD-9-CM OP codes) were ascertained and compared between the cohorts: catheterization (cardiac catheterization ICD-OP code: 37.21~37.23; coronary arteriography ICD-9-CM OP code: 88.55~88.57) and revascularizations (percutaneous transluminal coronary angioplasty (PTCA) with or without fibrinolytic therapy or intracoronary artery thrombolytic infusion ICD-OP code: 36.0X; other

heart revascularization ICD-OP code: 36.2X; coronary artery bypass graft (CABG) ICD-OP code: 36.1X). These were chosen in accordance with the *American College of Cardiology (ACC) /American Heart Association (AHA) Guidelines for the Management of Patients with Acute Myocardial Infarction* (Anbe et al., 1999).

**Table 6.4 ICD-9-CM OP codes for procedures**

| ICD-9-CM OP codes | Procedures |
|---|---|
| 36.XX | Operations on vessels of heart |
| 36.0X | Removal of coronary artery obstruction and insertion of stent |
| 36.XX | Bypass anastomosis for heart revascularization |
| 36.1X | Coronary bypass for heart revascularization |
| 37.21~37.23 | Diagnostic procedures on heart and pericardium |
| 88.55~88.57 | Coronary arteriography |

### 6.7 Outcome variables for the association of antipsychotic agents and AMI

Prescription instances of antipsychotic agents and other medications associated with AMI or the treatment of other cardiovascular diseases were identified from the datasets according to their registration numbers at the National Health Insurance Bureau. These medications were grouped according to the Anatomical Therapeutic Chemical (ATC) Classification System, a pharmaceutical coding system that divides different groups of medications according to the organ or system they act on (WHO, 2009), and which was published by the WHO Collaborating Centre for Drug Statistics Methodology (WHOCC, 2009). To measure and compare different antipsychotic agents, the technical unit of measurement called the Defined Daily Dose (DDD, or 'the assumed average maintenance dose per day for a drug used for its main indication in adults') (WHOCC, 2009) was applied. Groups of medications identified from the NHIRD in this thesis are summarized in **Table 6.5**.

**Table 6.5 Medications relevant in this thesis by ATC grouping**

| ATC codes | Procedures |
|---|---|
| N05A | Antipsychotic agents |
| N06A | Antidepressants |
| B01 | Antidiabetes agents |
| C03 | Diuretics |
| C07~C09 | Antihypertensives |
| C10 | Lipid modifying agents |

The ATC classification system and the DDD have been used in Norway since the early 1970s and are now recommended by the WHO for international use. Decisions on ATC classification and DDD assignment were established by 12 members of the International Working Group, drawn from the WHO Expert Advisory Panels for Drug Evaluation and for Drug Policies and Management, which itself drew from a wide range of geographical and professional backgrounds, including clinical pharmacology, clinical medicine, international public health, drug utilization and drug regulation. The Working Group continues to develop, discuss, and approve all new ATC codes and their DDDs. In addition, all DDDs are reviewed and revised semi-annually considering recent literature, and details are published on the website of the WHO Collaborating Centre for Drug Statistics Methodology and in the publication WHO Drug Information (WHOCC, 2009).

A DDD is usually established according to the maintenance dose of declared content (strength) of the product. All drugs have an individual DDD; for example, the DDD of chlorpromazine is 300mg, and that for haloperidol is 8mg. Thus, the ratio of DDD equivalent claims haloperidol be 37.5 times more potent than chlorpromazine. The main principle for assigning the DDDs for combinations of different

pharmacological products is based on counting the combination as one daily dose (WHOCC, 2009). An example from the WHO website for calculation of DDD for combination product is shown below:

Treatment with two products, each containing one active ingredient:

Product A: Tablets containing 20 mg of substance X (DDD = 20 mg)

Product B: Tablets containing 25 mg of substance Y (DDD = 25 mg)

The dosing schedule 1 tablet of A plus 1 tablet of B daily will be calculated as a consumption of 2 DDDs (WHOCC, 2009).

### 6.8 Application process and ethical considerations

The application for NHIRD datasets is only open to academic researchers in Taiwan and for research purposes only. The application process requires completing the application form alongside the researcher's personal profile, submitting the research proposal and lists of files requested, as well as signing an agreement to follow the Computer-Processed Personal Data Protection Law (http://www.winklerpartners.com/a/features/computerprocessed-personal-dat.php ) and related regulations of the Bureau of National Health Insurance and National Health Research Institutes (NHRI). All applications are reviewed under the committee of NHRI for approval of data release. Finally, analysis reported here received ethical approval by the Mackay Memorial Hospital Institutional Review Board, protocol number 10MMHIS056 (**Appendix 3**).

### 6.9 Data management procedures

The NHIRD resource provides valuable but complex datasets requiring a considerable degree of manipulation prior to analyses. The following processes were required to extract and prepare data:

1. The author sent an application requesting the PIMC and LHIRD2000 datasets that contained medical claim records from year 1996 to 2007 from the Institute of National Health Insurance Research in Taiwan (http://w3.nhri.org.tw/nhird//date_01.html) in year 2009. The following data files relevant to the study were embedded within the PIMC and the LHID2000 datasets:

(a) The registration files (capital letters in the brackets are the official initials for the files named by the NHIRD), which include:

- Registry for contracted beds ('**BED'**)
- Registry for contracted specialty services ('**DETA'**)

- Registry for contracted medical facilities (‘**HOSB’**)
- Supplementary registry for contracted medical facilities (‘**HOSX’**)
- Registry for board-certified specialists (‘**DOC’**)
- Registry for medical personnel (‘**PER’**)
- Registry for catastrophic illness patients (‘**HV’**)
- Registry for medical services (‘**HOX’**)
- Registry for drug prescriptions (‘**DRUG’**)
- Registry for beneficiaries (‘**ID’**)

(b) The Original Claim Data, which includes:

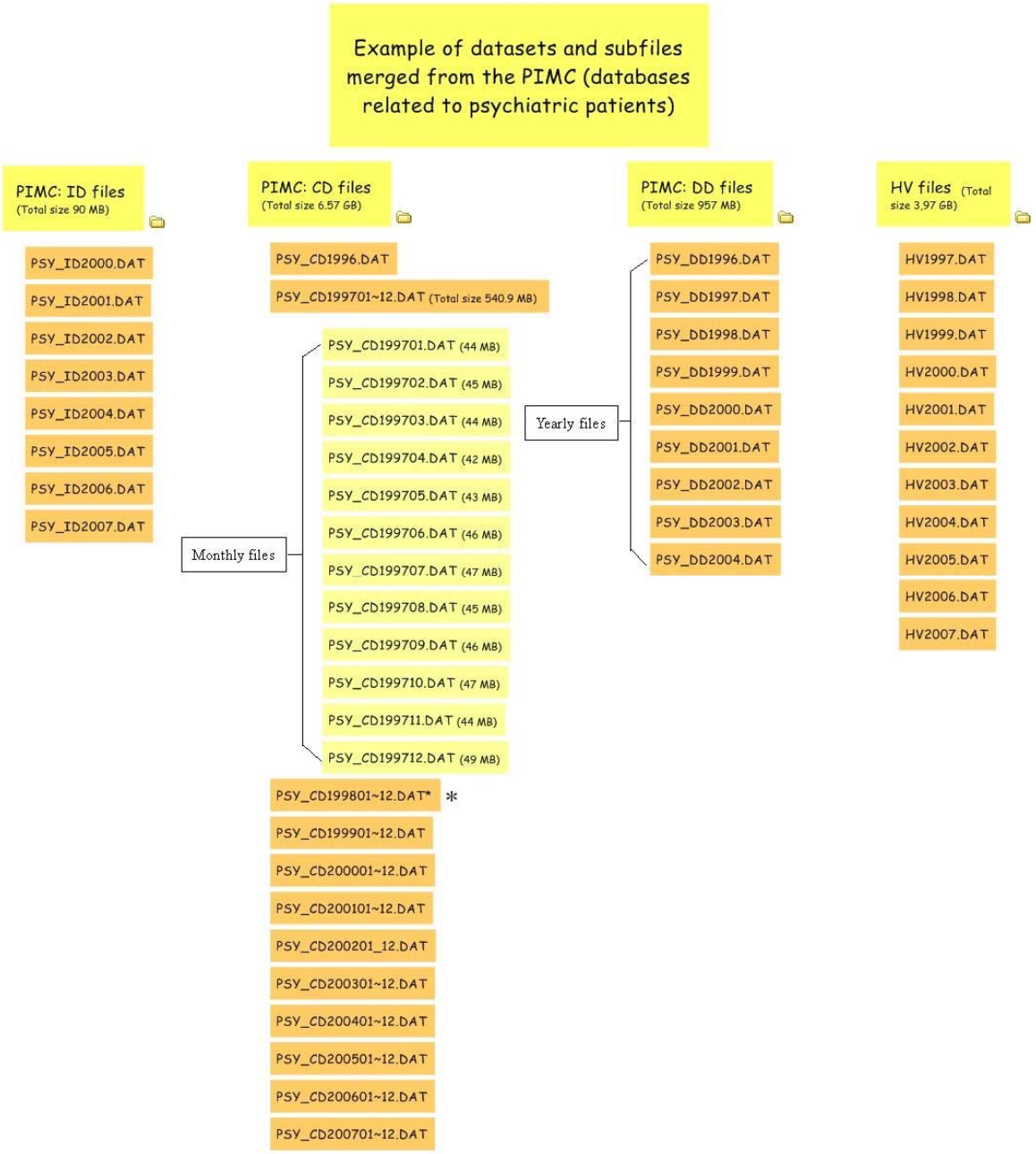
- Monthly claim summary for inpatient claims (‘**DT’**)
- Monthly claim summary for ambulatory care claims (‘**CT’**)
- Inpatient expenditures by admissions (‘**DD’**)
- Details of inpatient orders (‘**DO’**): its content includes service use, drugs prescribed, and intervention receipt during each hospitalization
- Ambulatory care expenditures by visits (‘**CD’**)
- Details of ambulatory care orders (‘**OO’**): its content includes service use, drugs prescribed, and intervention receipt during each ambulatory visit
- Expenditures for prescriptions dispensed at contracted pharmacies (‘**GD’**)
- Details of prescriptions dispensed at contracted pharmacies (‘**GO’**)

2. All the ‘Original Claim Data’ mentioned above were requested for every person registered as a PIMC beneficiary. For beneficiaries registered on the LHID2000, 300,000 out of the 1 million people were randomly selected (a simple random sample without stratification) (please see **Appendix 1** for the detailed list of 154 compact discs of data files applied).
3. Since each of the data files listed in **Appendix 1** is a compact disc composed of 12 or more monthly subfiles (each of which was approximately 85MB in size), the Macro Language of SAS was used to read in the above datasets and

to transform the ASCII files into SAS files in order to be used via the statistical software of SAS. A total of 154 data VCDs, 1475 subfiles, approximately 118GB were read.

4. Managing datasets: Horizontal merging of four different types of subsets (including Registry for beneficiaries (**'ID'**), Ambulatory care expenditures by visits (**'CD'**), Inpatient expenditures by admissions ('**DD'**), and Registry for catastrophic illness (severe mental or physical illness) patients subsets (**'HV'**)) into one single large data file were carried out separately for the PIMC (23,163,262 observations) and LHID2000 (51,607,426 observations) datasets. **Figure 6.3** illustrates an example of the datasets, yearly and monthly subfiles, and their sizes, merged from the PIMC, while **Figure 6.4** summarizes the main tasks of data management. **Appendix 2** lists the variables used for the analyses from the four main subsets of ('**ID**', '**CD**', '**DD**', and '**HV**'). Finally, **Figure 6.5** displays the variables used for merging and the merging details across different subsets.

**Figure 6.3 Example of datasets and subfiles used for data merging**

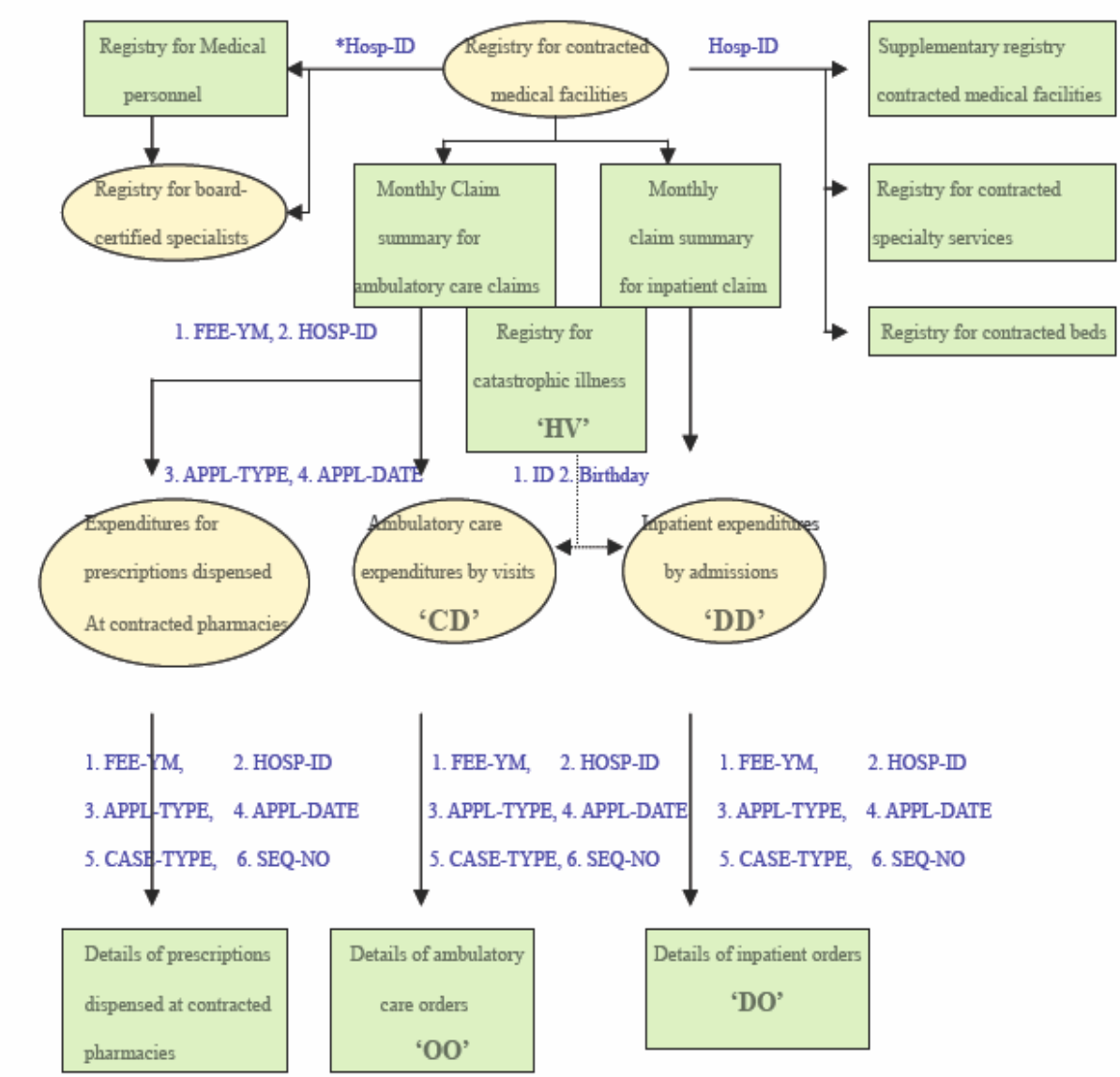



*Each of these yearly files contained 12 monthly subfiles, representing medical services given in each month of the year

**Figure 6.4 Procedures of data management and analysis**


5. Multiple observations per subject in the 'Registry for Beneficiaries (**ID**)' were transposed into one observation per subject containing the latest information regarding the beneficiary's demographic background. At this stage, two basic files had been created containing the subject's identification number and their demographic information for the 91,104 subjects from the PIMC dataset and 300,000 subjects from the LHID2000. These were therefore the 'primary source' for study and comparison subjects.

**Figure 6.5 Explanations of the variables needed for the merging process between different data files**




*Blue words represent variables used for merging

6. Data cleaning process: Information on gender, date of birth, level of household income, and geographic location of residence from the above basic files was checked using the following procedures:

(a) Information on the above demographic characteristics was sought from the four subsets of 'Registry ('**ID'**)', 'Ambulatory care ('**CD'**)', 'Admissions ('**DD'**)', and 'Registry for catastrophic illness patients subsets ('**HV'**)'.

(b) Information was cross-checked between these four subsets.

(c) If there was an inconsistency between subsets, the information from the 'Registry subset ('**ID'**)' was used as the final gold standard because it is the subset established to contain the basic personal profiles such as date of birth, status of insured or withdrawal from the registry, dates registration or withdrawal, the 'insured amount', and place of residence.

The above procedures were performed separately in the PIMC and the LHID2000 database.

7. Vertical merging was carried out of the 'Ambulatory care expenditures by visits ('**CD'**)' and the 'Inpatient expenditures by admissions ('**DD'**)' files from the PIMC (resulting in 25,001,803 observations and 82 variables in the newly vertically merged file) and the LHID2000 (resulting in a total 51,998,445 observations and 82 variables) in order to integrate all the medical services received either in outpatient or hospitalization sectors into one big file.

8. Horizontal merging was then carried out of the basic files containing subjects' identification numbers and demographic information with the abovementioned vertically-merged files containing observations of all medical visits between 1996 and 2007.

9. People were then identified with target diagnoses of mental disorders from the above files containing basic demographic information and observations of all medical visits:

(a) Applying the aforementioned inclusion, exclusion criteria, and hierarchical algorithm of psychiatric diagnoses, patients with schizophrenia or bipolar disorder were selected and labelled using ICD-9-CM codes matched with the principal diagnoses appearing in the '**CD**' and '**DD**' datasets each time people received medical services. At this stage, people with either the diagnosis of schizophrenia or bipolar disorder were allocated to the case cohort, whereas people without those diagnoses were allocated to the comparison cohort.

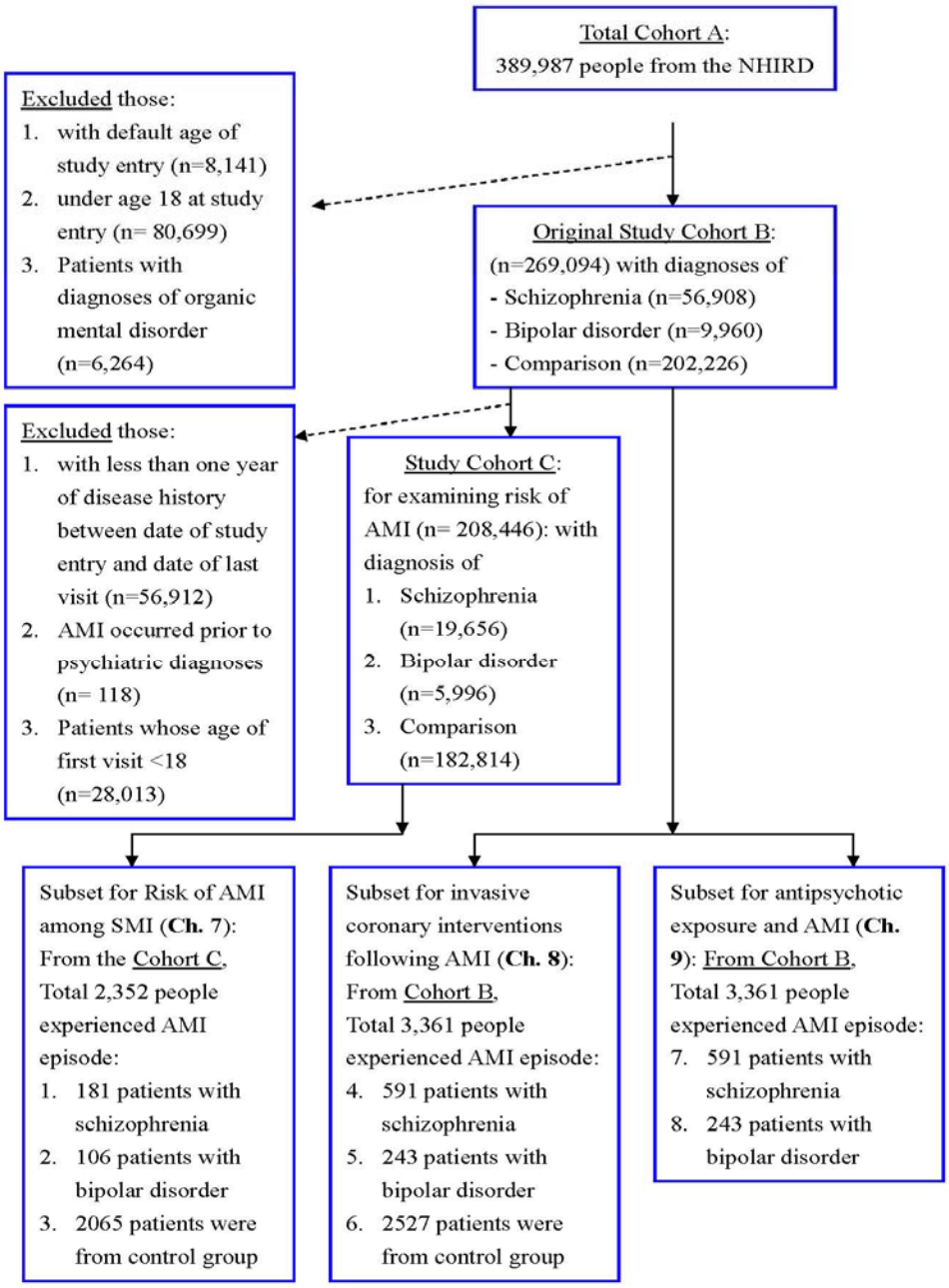
(b) Dates of receiving the first diagnoses of schizophrenia or bipolar disorder, or dates of first medical service received and recorded in the database were recorded as the date of study entry.

10. Ascertainment of acute myocardial infarction: The first diagnosis of AMI (ICD-9-CM 410.XX) from claim data of ambulatory care, emergency services, and hospitalization between 1996 and 2007 (from the vertically merged files of '**CD**' and '**DD**') was ascertained and a binary variable created.
11. In the case and comparison cohorts, any diagnoses were ascertained of previous cardiovascular risk factors or previous history of ischemic or coronary heart diseases received during the follow up period or before the occurrence of AMI.
12. The case and comparison cohorts were then vertically merged.
13. Information was obtained on intervention receipt, service use, and drugs prescribed during the AMI episode by merging the 'Details of inpatient orders ('**DO'**) data file' with the 'Inpatient expenditures by admissions ('**DD'**) data file', and the 'Ambulatory care expenditures by visits ('**CD'**) data file' with the 'Details of ambulatory care orders ('**OO'**) data file', using the identification number for each subject, the date of the index AMI episode, the hospital identification number, and the date that the hospital applied for treatment fees (see **Figure 6.5**). The above processes 9~11 involved the creation of accurate

and comprehensive code lists for every exposure, outcome, and covariates of interest, as well as searching these codes accurately to determine whether a subject had received a diagnosis, an investigation, or intervention, and if so, when.

14. As summarized in **Table 6.2,** the final created data file (or 'Total Cohort A' as in **Figure 6.6**) contained information of 389,987 people with or without SMI, and had 127 necessary binary, categorical, or continuous variables. As illustrated in **Figure 6.6**, two study cohorts were derived from 'Total Cohort A' for the purpose of examining different hypotheses in this thesis. The first one was 'Original Study Cohort B', which excluded people with missing dates of birth and age of study entry, those under age 18, and those with diagnoses of organic mental disorder. This 'Original Study Cohort B' was used for analyses in **Chapters 8~9**. In order to use Cox regression models to investigate the risk of AMI in people with or without SMI, the second study cohort, 'Study Cohort C', was obtained. This cohort was derived from 'Original Study Cohort B' with further exclusions of people who had less than one year of disease history before study entry (in order to obtain definite predictors from at least one year of records on medical utilization for Cox regressions), those whose AMI occurred prior to the first date of their psychiatric diagnosis, and those whose age of first visit was less than 18 years old. Further information on specific statistical analyses is provided in the following chapters.

**Figure 6.6 Algorithm on data retrieving**



# CHAPTER 7

# RELATIVE RISK OF ACUTE MYOCARDIAL INFARCITON IN PEOPLE WITH SCHIZOPHRENIA AND BIPOLAR DISORDER: A POPULATION-BASED STUDY

## 7.1 Objective

Despite high mortality associated with serious mental illness, risk of acute myocardial infarction (AMI) remains unclear, especially for patients with bipolar disorder. The main objective was to investigate the relative risk of acute myocardial infarction in adult patients with serious mental illness (SMI) in a national sample in Taiwan after adjusting for demographic characteristics, comorbid cardiovascular risk factors, and stratified by propensity score. The hypothesis was that the risk of AMI would be higher in the cases compared to controls.

## 7.2 Method

### 7.2.1 Case cohort

The case cohort comprised patients with schizophrenia or bipolar disorder identified from the PIMC and the LHIRD2000 (details of procedures for identifying the case cohort are described in **Chapter 6.2 and 6.3**). Their date of study entry was defined as the date of receiving their first psychiatric diagnosis. To obtain valid information on medical history prior to their study entry, the case cohort was restricted to those whose first medical visit (i.e. that which was not due to AMI) occurred at least one year prior to their first psychiatric diagnosis.

### 7.2.2 Comparison cohort

The comparison cohort were people of general population selected from the LHIRD2000 applying the inclusion and exclusion criteria (details described in **Chapter 6.2 and 6.3**). The time origin of study entry for the comparison cohort was defined as one year after the date of the first medical visit recorded in the database.

### 7.2.3 Statistical analysis

Statistical analyses were performed in three stages. Descriptive analyses were carried

out initially. Next, Cox regression models were used to compare the risk of AMI in people with or without serious mental illness. Third, after the primary analysis, the Cox regression model was performed again stratified by subgroups of propensity scores as a secondary analysis to control for differences in patients' characteristics between 'case' and 'control' groups. This was instituted in response to comments from external reviewers on a submitted research paper containing these findings.

As described individually in **Chapter 6.5** and summarized in **Table 6.2**, factors widely recognized to be associated with increased risk of AMI include diabetes mellitus, hypertension, hyperlipidaemia, male gender, tobacco use, family history of atherosclerotic arterial disease, low socioeconomic status, stress, and negative emotions (Cotran RS, 1994; Druss & Rosenheck, 2000; Druss et al., 2002; Lin et al., 2006; Nyboe et al., 1989). Although some of the above factors could not be obtained (such as tobacco use, family history of coronary diseases, precipitating stressors, or negative emotions), measurements available for extraction from this dataset were included and adjusted for in three different models in order to investigate individual effects on the association of interest. Model 1 adjusted for age at study entry; model 2 adjusted for all demographic characteristics; and model 3 adjusted for all the demographic characteristics and cardiovascular risk factors. Detailed statistical procedures were as follows:

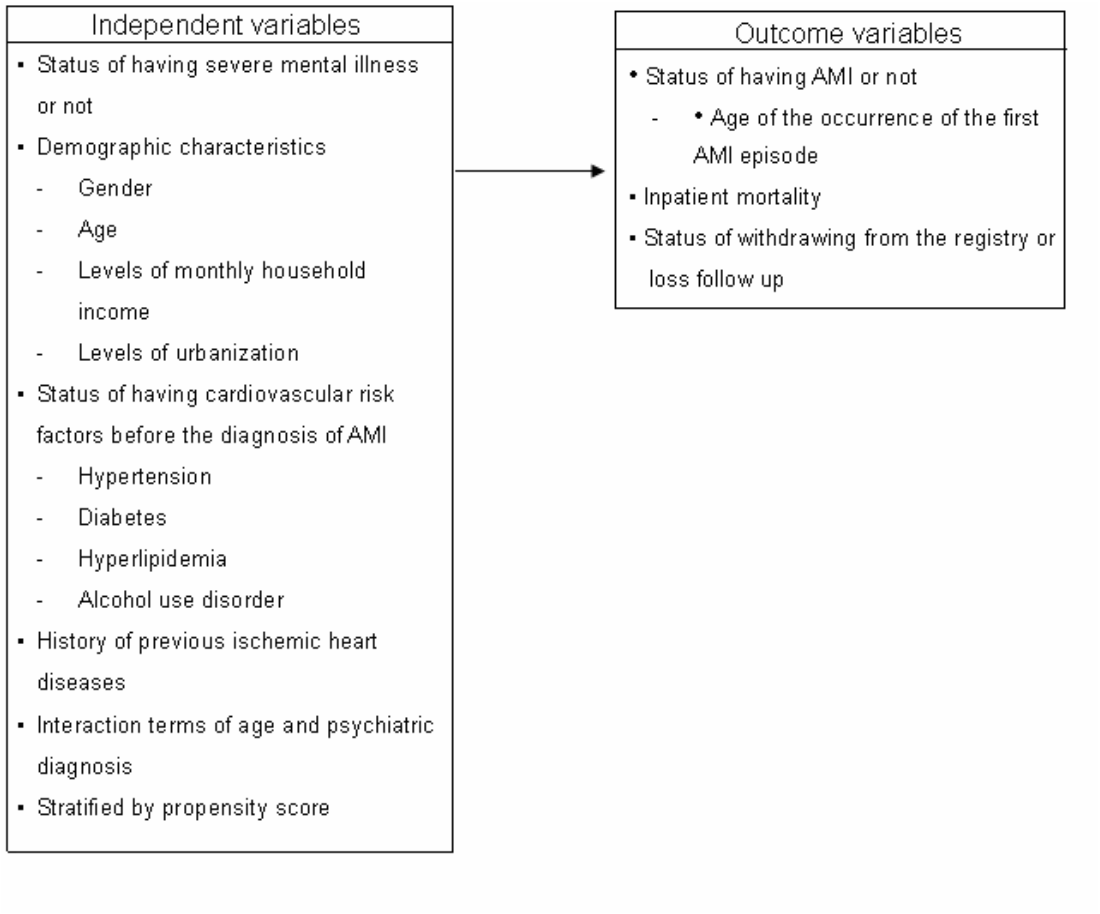
I. Descriptive analysis

SAS version 9 for Windows (SAS Institute, Cary, NC) was used for data management and analysis. The frequencies of target disorders were displayed. Pearson's chi-squared tests were used for categorical variable comparisons. T-tests and one-way analyses of variance (ANOVA) were used to investigate mean differences in age of psychiatric disorder and AMI.

II. Cox regression analyses

Cox models were used to estimate hazard ratios for rate outcomes and to adjust for other covariates. The starting points were the time of first psychiatric diagnosis between 1996 and 2007 in the case cohort, and the time of first medical visit for the comparison cohort – i.e. individuals who received their first mental disorder diagnosis after AMI were excluded. Collinearity between variables was checked prior to their inclusion in regression models. Censoring points were the end of follow up or the date of withdrawal from the registry (a proxy for mortality). Hazard ratios and 95% confidence intervals were obtained for the outcome stratified by gender and age groups. Tests of effect modification for the associations of interest were restricted *a priori* to age and gender, age group at study entry being entered as an ordinal variable on one degree of freedom, on the assumption that interactions of interest would show linear relationships with age. Proportional hazards assumptions were checked from Kaplan-Meier survival curves. Sensitivity analyses were carried out, restricting the study sample to those who had their first AMI diagnoses occurred after 07.01.2001 (i.e. during the latter half of the surveillance period) on the assumption that this would enrich the AMI outcome with 'first ever' events. **Figure 7.1** illustrates the independent and outcome variables used in this part of the analysis.

**Figure 7.1 Concept for the analysis of the risk of AMI in people with serious mental illness**



III. Cox regression analyses stratified by propensity scores

Further Cox regression analyses were then constructed, stratified by propensity scores to balance demographic and clinical characteristics between case and comparison cohorts (Joffe & Rosenbaum, 1999). The theory behind this operation is that when one case (i.e. a person with a psychiatric diagnosis) is found to have the same propensity score, or is within the same propensity stratum as one comparison subject (i.e. someone without a psychiatric diagnosis), it is assumed with more confidence that these two subjects have been 'randomly' assigned to each cohort on the basis of having equal chances of assignation as a case or comparison subject (D'Agostino, 1998). Propensity scores are generally calculated based on the covariates that affect the allocation to case or comparison cohorts (Millier et al., 2011). Relevant covariates for estimating the propensity score used in this study are listed in **Table 7.1**.

**Table 7.1 Summary of covariates used for calculating propensity scores for each subject**

| **Table 7.1 Summary of covariates used for calculating propensity scores for each subject** | | |
|---|---|---|
| Age at index date (i.e. the date one year after study entry) | 5 groups based on its distribution | 1= 18-34<br>2= 35-44<br>3= 45-54<br>4= 55-64<br>5= 65 and above |
| Gender | 2 groups | 0= Female<br>1= Male |
| Levels of monthly income | 4 groups based on previous literature | 0= NT$ 0<br>1= NT$ 1~15840<br>2= NT$ 15841 ~ 25000<br>3= ≧NT$ 25001 |
| Levels of urbanization of residence | 5 groups based on the locations | 1= most urbanized<br>2<br>3<br>4<br>5= least urbanized |
| Having received diagnosis of cardiovascular risk factors prior to index date | 2 groups on each diagnosis based on having this diagnosis or not | 0 = ‘No’<br>1 = ‘Yes’ |
| History of visiting psychiatric department before index date | 2 groups based on having the episode or not | 0 = ‘No’<br>1 = ‘Yes’ |
| Hospital levels of visits before index date | 4 groups based on the levels of hospital | 1 = Medical center<br>2 = Regional hospital<br>3 = District hospital<br>4 = Others |

From the literature (Lo, 2004), the estimate of propensity score ($\hat{P}_S$) is:

$$\hat{P}_S = \frac{1}{1 + e^{-(a + \sum_{i=1}^{k} b_i x_{ij})}}$$

So,

$$\ln\left(\frac{\hat{P}_s}{1-\hat{P}_s}\right) = a + \sum_{i=1}^{k} b_i x_{ij}$$

Where,

*x* are independent variables, eg. age, gender…

*a* is the estimate of the intercept

*b* is the coefficient for the interaction that achieve significant level (0.001) between variables

*e* stands for exponent

ln stands for natural log

Referring to the functions mentioned above, the propensity score for each patient in this study was calculated using logistic regression based on covariates listed in **Table 7.1** as independent predictors affecting the receipt of psychiatric diagnosis (i.e. the allocation of case or comparison cohort). This propensity score corresponded to the probability of being assigned to the case or control group. Definitions for the date of study entry were the date of receiving the first psychiatric diagnosis for the case group, and the date of first medical visit appearing in the records (from 1996 to 2007) for the comparison group.

Second, individuals were stratified by 20$^{th}$, 30$^{th}$, 40$^{th}$ percentiles of increasing propensity score, so that in each stratum, the probability of being assigned to case or

control group was similar, as well as having enough AMI subjects in each cohort to be able to analyze. Collinearity between variables was checked prior to their inclusion in regression models (Kim et al., 2011).

Third, having matched the sample by propensity score stratification, Cox regression analyses with propensity score stratification were carried out to compare rates of AMI between the propensity-matched case and comparison cohorts. Hazard ratios and 95% confidence intervals were obtained for the outcome and were stratified by gender and age groups. Adjustments for age of study entry, history of medical disorder prior to study entry, and other covariates were also performed.

## 7.3 Results

### 7.3.1 Samples included

Among the 91,104 individuals from the PIMC and 300,000 comparison samples from the LHID2000, 1,117 individuals (734 had diagnosis of schizophrenia and 156 had bipolar disorder) appeared in both datasets. There were 2,567 and 2,800 individuals from the LHID2000 that had been diagnosed with schizophrenia or bipolar disorder, respectively.

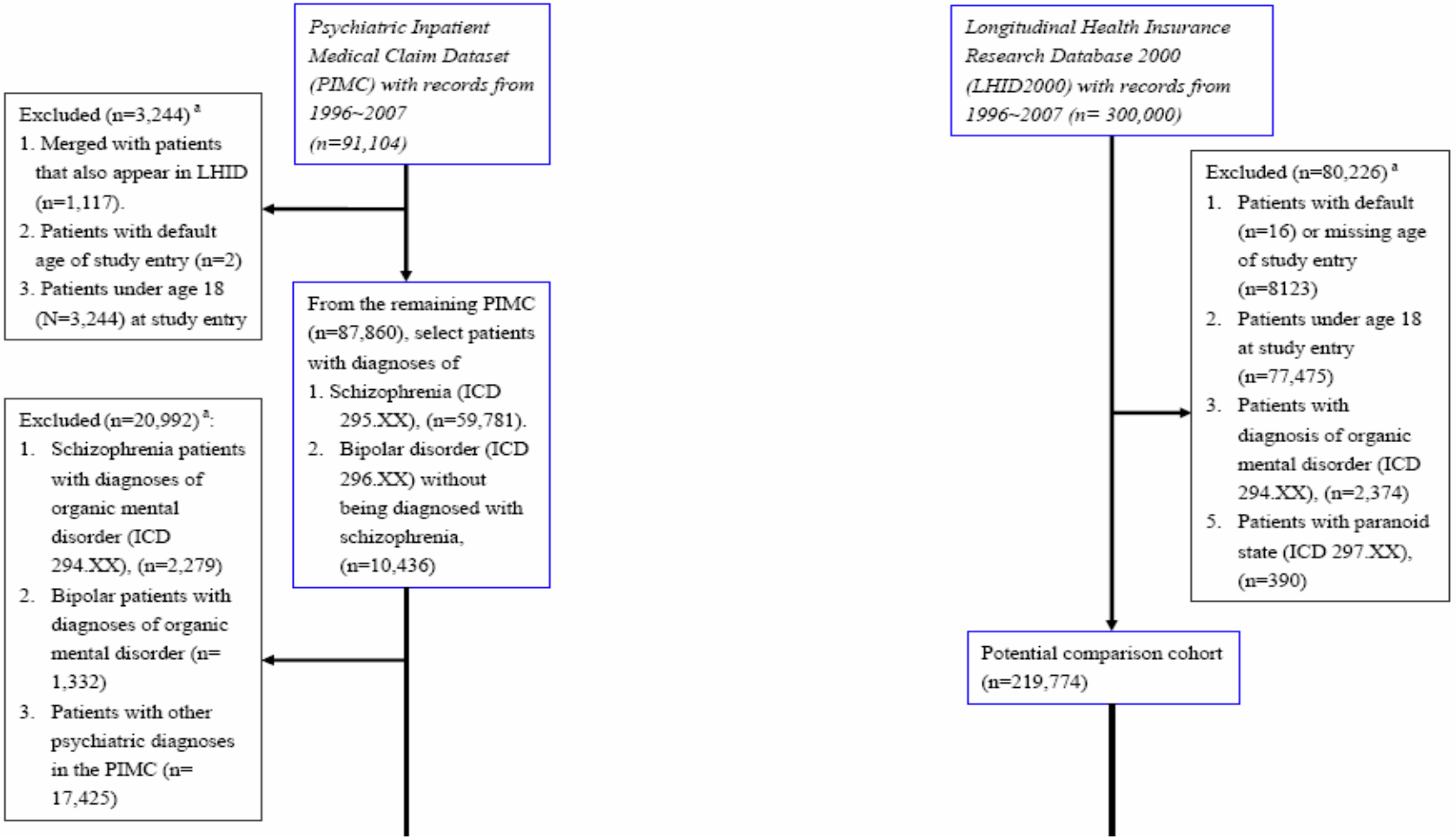
After applying inclusion and exclusion criteria, there were 208,466 adults from the PIMC and LHID2000 datasets included, of whom 19,656 and 5,996 had a diagnosis of schizophrenia and bipolar disorder respectively during the 12-year period, with 182,814 comparison subjects. Among the individuals with mental disorders of interest, 18,627 (94.8%) of those with schizophrenia, and 5,975 (99.6%) of those with bipolar disorder were contained on the PIMC register – i.e. had received their psychiatric diagnosis in the context of a hospitalization episode between 1996 and 2000. Of the 202,226 people on the LHID, 72 (46.5%) of all 155 patients with bipolar disorder were also on the PIMC (i.e. cases that had received hospitalization), compared to 164 (12.5%) of all 1,317 patients with schizophrenia. A flow chart detailing selection processes is displayed in **Figure 7.3**.

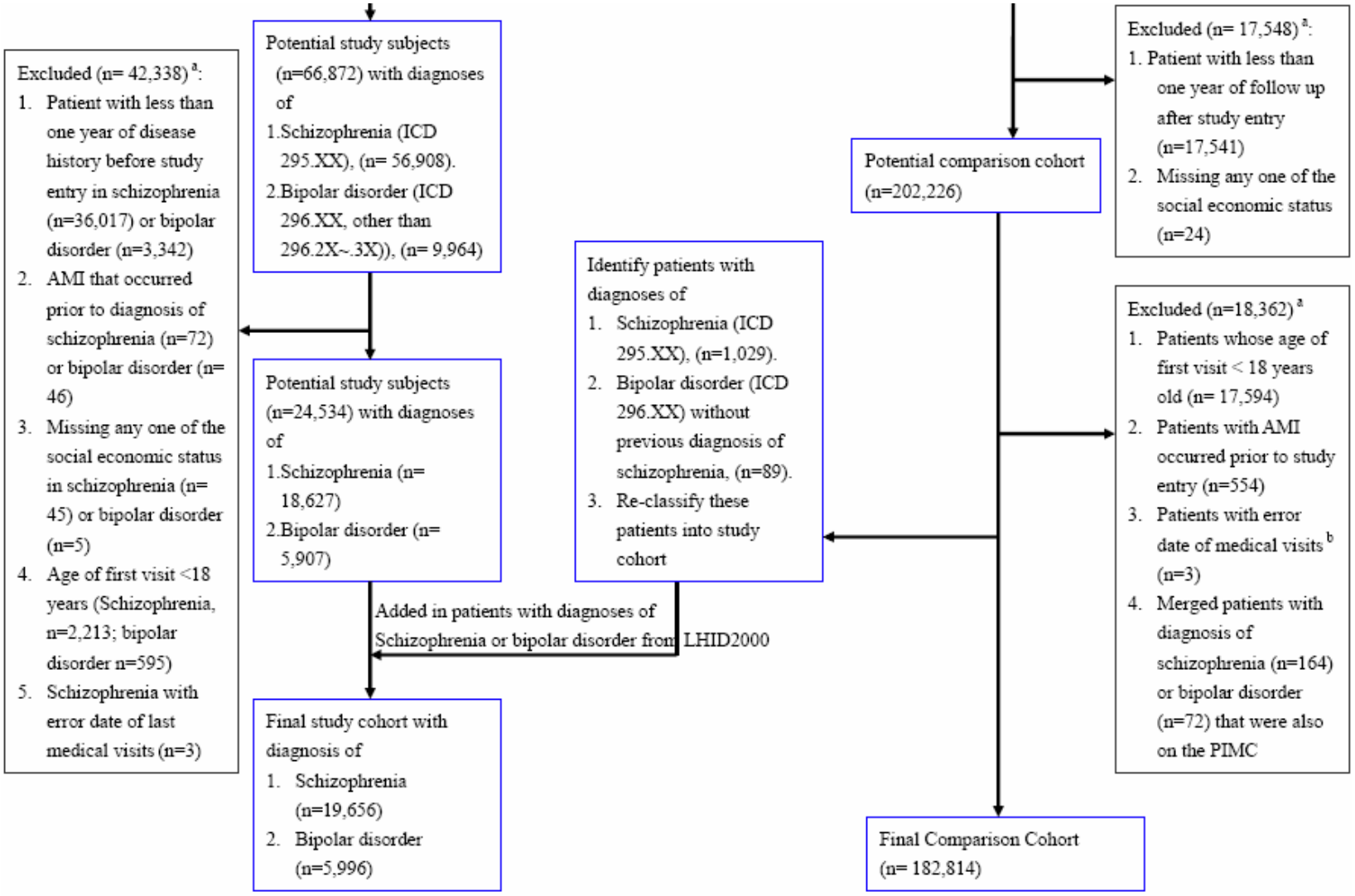
### 7.3.2 Missing data

As specified in **Figure 7.3**, eighteen individuals were excluded from the beginning of data management because of missing information on date of birth. 8,123 individuals from the LHID2000 were excluded because they never had any medical visit from year 1996 to 2007, and therefore, did not have a date for study entry (defined as first medical visit during the follow up period). Finally, 57 individuals were excluded before entering the analysis due to missing any of the information on gender, or

levels of urbanization or income.

**Figure 7.2 Flow chart illustrating selection of case and comparison cohorts from patients registered in Taiwan's National Health Insurance Research Database**




Potential study subjects (n=66,872) with diagnoses of
1.Schizophrenia (ICD 295.XX), (n= 56,908).
2.Bipolar disorder (ICD 296.XX, other than 296.2X~.3X)), (n= 9,964)
Excluded (n= 42,338) [a]:
1. Patient with less than one year of disease history before study entry in schizophrenia (n=36,017) or bipolar disorder (n=3,342)
2. AMI that occurred prior to diagnosis of schizophrenia (n=72) or bipolar disorder (n= 46)
3. Missing any one of the social economic status in schizophrenia (n= 45) or bipolar disorder (n=5)
4. Age of first visit <18 years (Schizophrenia, n=2,213; bipolar disorder n=595)
5. Schizophrenia with error date of last medical visits (n=3)
Potential study subjects (n=24,534) with diagnoses of
1.Schizophrenia (n= 18,627)
2.Bipolar disorder (n= 5,907)
Identify patients with diagnoses of
1. Schizophrenia (ICD 295.XX), (n=1,029).
2. Bipolar disorder (ICD 296.XX) without previous diagnosis of schizophrenia, (n=89).
3. Re-classify these patients into study cohort
Added in patients with diagnoses of Schizophrenia or bipolar disorder from LHID2000
Final study cohort with diagnosis of
1. Schizophrenia (n=19,656)
2. Bipolar disorder (n=5,996)
Potential comparison cohort (n=202,226)
Excluded (n= 17,548) [a]:
1. Patient with less than one year of follow up after study entry (n=17,541)
2. Missing any one of the social economic status (n=24)
Excluded (n=18,362) [a]
1. Patients whose age of first visit < 18 years old (n= 17,594)
2. Patients with AMI occurred prior to study entry (n=554)
3. Patients with error date of medical visits [b] (n=3)
4. Merged patients with diagnosis of schizophrenia (n=164) or bipolar disorder (n=72) that were also on the PIMC
Final Comparison Cohort (n= 182,814)

[a]The n for these exclusion criteria add up to more than the total n because some patients met more than one exclusion criterion
[b] Including age at last visit > 120 years old (n=2), unreasonable date of last visit (n= 1)

### 7.3.3 Sample characteristics

**Table 7.2** summarises the characteristics of the cohorts. Significant differences were found in the mean ages at study entry of the three groups (ANOVA F 693.10, df 2, p<0.001) and in all categorical variables (including age group) between people with and without serious mental illness (all p-values <0.001) from chi-squared tests. On observation, individuals with schizophrenia had a higher male predominance and lower income, and were more likely have past history of diabetes, hyperlipidaemia and alcohol use disorders prior to study entry compared to the comparison group. On the other hand, people diagnosed with bipolar disorder had a higher female predominance, higher proportions living in more urbanized areas compared to schizophrenia, and a higher likelihood of having previous history of the medical diagnoses of interest prior to study entry than the comparison group.

In the combined cohorts of 208,466 people, 2,352 (1.13%) had experienced at least one AMI episode during the 12-year follow up period: 181 (0.92%) in those with schizophrenia, 106 (1.77%) in those with bipolar disorder, and 2,065 (1.13%) in the comparison cohort. The mean (SD) age at recorded AMI was 60.6 (16.4) years for people with schizophrenia, 65.1 (15.1) years in people with bipolar disorder, and 66.5 (13.7) years in the comparison cohort. The mean age at the index AMI was 5.9 (95% CI 3.8~8.0,) years lower for schizophrenia compared to comparison subjects (t 5.5, df 2244, p <0.001), 1.4 (95% CI -1.2~.4.1) years lower in bipolar disorder compared to comparison subjects (t 1.05, df 2169, p =0.29), and 4.5 (95% CI 0.6~.8.3) years lower for schizophrenia compared to bipolar disorder (t 2.29, df 285, p =0.02).

**Table 7.2 Baseline between-cohort comparison of demographic characteristics and cardiovascular risk factors**

| | No serious mental illness (n= 182,814) | Schizophrenia (n= 19,656) | Bipolar disorder (n= 5,996) | Test statistic, degree of freedom (df), P value |
|---|---|---|---|---|
| Mean (SD) age at study entry | 43.7 (15.8) | 39.7 (14.6) | 46.5 (16.4) | F 693.1, df 2, p<0.001 |
| Age group at study entry (%) | | | | $\chi^2$ 1501.6, df 8, p<0.001 |
| 18~34 | 35.3 | 46.2 | 29.4 | |
| 35~44 | 24.6 | 25.6 | 24.8 | |
| 45~54 | 16.7 | 13.4 | 17.0 | |
| 55~64 | 10.7 | 6.4 | 11.3 | |
| 65 and above | 12.8 | 8.5 | 17.6 | |
| Gender (%) | | | | $\chi^2$ 169.9, df 2, p<0.001 |
| Men | 50.6 | 54.6 | 45.9 | |
| Women | 49.4 | 45.5 | 54.1 | |
| Levels of urbanization (%) | | | | $\chi^2$ 291.3, df 8, p<0.001 |
| 1 (most urbanized) | 31.3 | 28.0 | 33.4 | |
| 2 | 29.2 | 29.6 | 29.6 | |
| 3 | 17.5 | 17.4 | 14.1 | |
| 4 | 13.1 | 13.0 | 12.2 | |
| 5 (least urbanized) | 9.0 | 12.0 | 10.8 | |
| Monthly income (%) | | | | $\chi^2$ 3993.6, df 6, p<0.001 |

| | | | | |
|---|---|---|---|---|
| NT 0 | 23.3 | 23.4 | 27.1 | |
| NT$ 1~15840 | 18.6 | 34.9 | 24.8 | |
| NT$ 15841 ~ 25000 | 39.4 | 34.8 | 34.8 | |
| ≧NT$ 25001 | 18.7 | 7.0 | 13.3 | |
| History of angina (%) | 1.9 | 3.3 | 12.4 | $\chi^2$ 2844.5, df 2, p<0.001 |
| History of hypertension (%) | 7.3 | 7.4 | 23.9 | $\chi^2$ 2234.9, df 2, p<0.001 |
| History of diabetes (%) | 2.4 | 5.7 | 15.0 | $\chi^2$ 3678.9, df 2, p<0.001 |
| History of hyperlipidemia (%) | 2.8 | 4.3 | 14.1 | $\chi^2$ 2360.7, df 2, p<0.001 |
| History of alcohol use disorders (%) | 0.3 | 8.4 | 17.1 | $\chi^2$ 17974.7, df 2, p<0.001 |
| Acute myocardial infarction (%) | 1.1 | 0.9 | 1.8 | $\chi^2$ 29.6, df 2, p<0.001 |
| History of visiting psychiatric department before study entry (%) | 2.5 | 79.1 | 96.3 | $\chi^2$ 135852, df 2, p<0.001 |
| Hospital levels of visits before study entry (%) | | | | |
| Medical centers | 42.2 | 60.7 | 80.3 | $\chi^2$ 50224.3, df 2, p<0.001 |
| Regional hospitals | 46.5 | 72.2 | 79.7 | $\chi^2$ 53180.3, df 2, p<0.001 |
| District hospitals | 61.0 | 71.8 | 79.4 | $\chi^2$ 18946.3, df 2, p<0.001 |
| Primary care | 97.4 | 92.8 | 97.1 | $\chi^2$ 1626.4, df 2, p<0.001 |

### 7.3.4 Results of Cox regression

Hazard ratios of AMI comparing people with or without serious mental illness were calculated from multivariate Cox regression and are summarized in **Table 7.3**. Addition of hypertension, diabetes and hyperlipidaemia diagnoses to the models substantially attenuated the hazard ratios for both disorders. Age-modification was found in fully adjusted model with hazard ratios for older age x disorder interaction terms of 0.88 (95% CI 0.78~0.99, p=0.046) in schizophrenia and bipolar disorder 0.73 (95% CI 0.61~0.87, p<0.001); indicating a stronger excess risk in younger individuals with serious mental illness. Gender- interaction terms in the fully adjusted model were male gender x disorder: 0.91 (95% CI 0.66~1.25, p=0.57) and 0.67 (95% CI 0.45~1.00, p=0.05) for people with schizophrenia and bipolar disorder, respectively. Three-way (age group x gender x disorder) interaction terms were tested in fully adjusted models. Such interaction was found to be significant in people with bipolar disorder (0.93, 95% CI 0.87~0.99, p=0.02) but not in schizophrenia (0.98, 95% CI 0.93~1.03, p=0.35).

**Table 7.3 (a) Hazard ratios (HR) of AMI in people with and without schizophrenia**

| | Numbers of AMI events in people with schizophrenia (n=181) | Numbers of AMI in the general population (n=2,065) | Unadjusted HR | Model 1 | Model 2 | Model 3 |
|---|---|---|---|---|---|---|
| Male (Age groups ) | | | | | | |
| Total male | 112 | 1302 | 1.11 ( 0.92 ~ 1.35 ) | 1.05 ( 0.87 ~ 1.28 ) | 1.03 ( 0.85 ~ 1.26 ) | 0.90 ( 0.74 ~ 1.01 ) |
| 18~44 | 13 | 52 | 1.34 ( 0.92 ~ 1.96 ) | 1.06 ( 0.72 ~ 1.56 ) | 1.06 ( 0.72 ~ 1.57 ) | 0.97 ( 0.65 ~ 1.44 ) |
| 45~54 | 19 | 133 | 1.01 ( 0.63 ~ 1.63 ) | 0.95 ( 0.59 ~ 1.53 ) | 0.93 ( 0.58 ~ 1.51 ) | 0.76 ( 0.47 ~ 1.24 ) |
| 55~64 | 19 | 256 | 1.01 ( 0.59 ~ 1.73 ) | 1.00 ( 0.59 ~ 1.72 ) | 0.97 ( 0.57 ~ 1.66 ) | 0.82 ( 0.48 ~ 1.42 ) |
| 65 and above | 61 | 861 | 1.01 ( 0.75 ~ 1.35 ) | 1.18 ( 0.87 ~ 1.59 ) | 1.16 ( 0.86 ~ 1.56 ) | 1.01 ( 0.75 ~ 1.37 ) |
| Female (Age groups) | | | | | | |
| Total female | 69 | 763 | **1.42 ( 1.11 ~ 1.82 )** | 1.22 ( 0.95 ~ 1.56 ) | 1.22 ( 0.95 ~ 1.56 ) | 1.02 ( 0.79 ~ 1.32 ) |
| 18~44 | 9 | 14 | **2.65 ( 1.52 ~ 4.62 )** | **2.34 ( 1.33 ~ 4.09 )** | **2.35 ( 1.34 ~ 4.12 )** | **2.18 ( 1.23 ~ 3.87 )** |
| 45~54 | 8 | 42 | **2.00 ( 1.21 ~ 3.32 )** | **1.94 ( 1.16 ~ 3.22 )** | **1.95 ( 1.17 ~ 3.26 )** | 1.49 ( 0.87 ~ 2.56 ) |
| 55~64 | 18 | 96 | 1.11 ( 0.63 ~ 1.95 ) | 1.07 ( 0.61 ~ 1.88 ) | 1.09 ( 0.62 ~ 1.91 ) | 0.93 ( 0.53 ~ 1.66 ) |
| 65 and above | 34 | 611 | 0.88 ( 0.57 ~ 1.37 ) | 0.85 ( 0.55 ~ 1.32 ) | 0.85 ( 0.55 ~ 1.32 ) | 0.69 ( 0.44 ~ 1.08 ) |

| | | | | | | |
|---|---|---|---|---|---|---|
| All (Age groups) | | | | | | |
| Total | 181 | 2065 | **1.23 ( 1.05 ~ 1.43 )** | 1.10 ( 0.95 ~ 1.29 ) | 1.09 ( 0.94 ~ 1.27 ) | 0.93 ( 0.80 ~ 1.09 ) |
| 18~44 | 22 | 66 | **1.67 ( 1.22 ~ 2.29 )** | **1.38 ( 1.01 ~ 1.90 )** | **1.41 ( 1.03 ~ 1.94 )** | 1.29 ( 0.94 ~ 1.79 ) |
| 45~54 | 27 | 175 | 1.26 ( 0.89 ~ 1.77 ) | 1.20 ( 0.85 ~ 1.69 ) | 1.20 ( 0.85 ~ 1.70 ) | 0.95 ( 0.67 ~ 1.37 ) |
| 55~64 | 37 | 352 | **1.75 ( 1.17 ~ 2.60 )** | 0.99 ( 0.67 ~ 1.47 ) | 0.98 ( 0.66 ~ 1.45 ) | 0.84 ( 0.57 ~ 1.25 ) |
| 65 and above | 95 | 1472 | 1.03 ( 0.70 ~ 1.51 ) | 1.06 ( 0.83 ~ 1.35 ) | 1.05 ( 0.82 ~ 1.35 ) | 0.90 ( 0.70 ~ 1.15 ) |



Model 1: Adjusted for age at study entry

Model 2: Adjusted for gender (where not stratified), age at study entry, levels of income, levels of urbanization, and hospital levels before study entry

Model 3: Adjusted for gender (where not stratified), age at study entry, levels of income, levels of urbanization, previous coronary heart disease hypertension, diabetes, and hyperlipidaemia

**Table 7.3 (b) Hazard ratios (HR) of AMI in people with and without bipolar disorder**

| | Numbers of AMI events in people with bipolar disorder (n=106) | Numbers of AMI in the general population (n=2,065) | Unadjusted HR | Model 1 | Model 2 | Model 3 |
|---|---|---|---|---|---|---|
| Male (Age groups ) | | | | | | |
| Total male | 54 | 1302 | 0.94 ( 0.72 ~ 1.24 ) | 1.10 ( 0.84 ~ 1.44 ) | 1.08 ( 0.82 ~ 1.42 ) | **0.72 ( 0.54 ~ 0.97 )** |
| 18~44 | 2 | 52 | 1.75 ( 0.90 ~ 3.42 ) | 1.71 ( 0.87 ~ 3.34 ) | 1.75 ( 0.90 ~ 3.42 ) | 1.13 ( 0.55 ~ 2.35 ) |
| 45~54 | 7 | 133 | 0.93 ( 0.41 ~ 2.09 ) | 0.91 ( 0.41 ~ 2.05 ) | 0.93 ( 0.41 ~ 2.09 ) | 0.52 ( 0.23 ~ 1.22 ) |
| 55~64 | 6 | 256 | 1.37 ( 0.75 ~ 2.51 ) | 1.37 ( 0.75 ~ 2.51 ) | 1.37 ( 0.75 ~ 2.51 ) | 0.75 ( 0.39 ~ 1.43 ) |
| 65 and above | 11 | 861 | 0.92 ( 0.63 ~ 1.34 ) | 1.00 ( 0.69 ~ 1.47 ) | 0.92 ( 0.63 ~ 1.34 ) | 0.74 ( 0.50 ~ 1.11 ) |
| Female (Age groups) | | | | | | |
| Total female | 52 | 763 | **1.92 ( 1.45 ~ 2.54 )** | **1.69 ( 1.28 ~ 2.25 )** | **1.69 ( 1.27 ~ 2.24 )** | 0.91 (0.66 ~ 1.26) |
| 18~44 | 2 | 14 | **4.45 ( 2.20 ~ 8.99 )** | **4.34 ( 2.15 ~ 8.78 )** | **4.32 ( 2.13 ~ 8.74 )** | **2.40 ( 1.04 ~ 5.55 )** |
| 45~54 | 7 | 42 | **2.44 ( 1.23 ~ 4.84)** | **2.43 ( 1.22 ~ 4.82)** | **2.40 ( 1.21 ~ 4.78)** | 1.38 ( 0.63 ~ 3.04) |
| 55~64 | 9 | 96 | **2.31 ( 1.37 ~ 3.92 )** | **2.27 ( 1.34 ~ 3.85 )** | **2.25 ( 1.33 ~ 3.82 )** | 0.91 ( 0.48 ~ 1.70 ) |
| 65 and above | 34 | 611 | 1.26 ( 0.79 ~ 2.02 ) | 1.06 ( 0.66 ~ 1.70 ) | 1.05 ( 0.65 ~ 1.68 ) | 0.62 ( 0.37 ~ 1.04 ) |
| All (Age groups) | | | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| Total | 106 | 2065 | **1.27 ( 1.05 ~ 1.54 )** | **1.29 ( 1.06 ~ 1.56 )** | **1.28 ( 1.05 ~ 1.56 )** | **0.77 ( 0.63 ~ 0.96 )** |
| 18~44 | 4 | 66 | **2.34 ( 1.45 ~ 3.77 )** | **2.24 ( 1.39 ~ 3.62 )** | **2.24 ( 1.39 ~ 3.62 )** | 1.40 ( 0.82 ~ 2.40 ) |
| 45~54 | 14 | 175 | 1.33 ( 0.79 ~ 2.24 ) | 1.31 ( 0.78 ~ 2.21 ) | 1.31 ( 0.78 ~ 2.20 ) | 0.68 ( 0.39 ~ 1.21 ) |
| 55~64 | 15 | 352 | **1.75 ( 1.18 ~ 2.60 )** | **1.73 ( 1.16 ~ 2.57 )** | **1.69 ( 1.13 ~ 2.50 )** | 0.83 ( 0.53 ~ 1.29 ) |
| 65 and above | 73 | 1472 | 1.06 ( 0.79 ~ 1.42 ) | 1.03 ( 0.76 ~ 1.38 ) | 1.03 ( 0.77 ~ 1.38 ) | **0.69 ( 0.51 ~ 0.95 )** |



Model 1: Adjusted for age at study entry

Model 2: Adjusted for gender (where not stratified), age at study entry, levels of income, levels of urbanization, and hospital levels before study entry

Model 3: Adjusted for gender (where not stratified), age at study entry, levels of income, levels of urbanization, previous coronary heart disease hypertension, diabetes, and hyperlipidaemia

**Figures 7.3(a)** and **(b)** summarize age and gender stratified models for schizophrenia and bipolar disorder. It was observed that risks of AMI in the two serious mental illness cohorts were raised in the groups less than 45 years of age for women with schizophrenia or bipolar disorder.

**Figure 7.3 (a) Age-stratified hazard ratios and 95% confidence intervals of AMI in men with or without schizophrenia or bipolar disorder (adjusted for age at study entry, levels of income and urbanization, cardiovascular risk factors)**

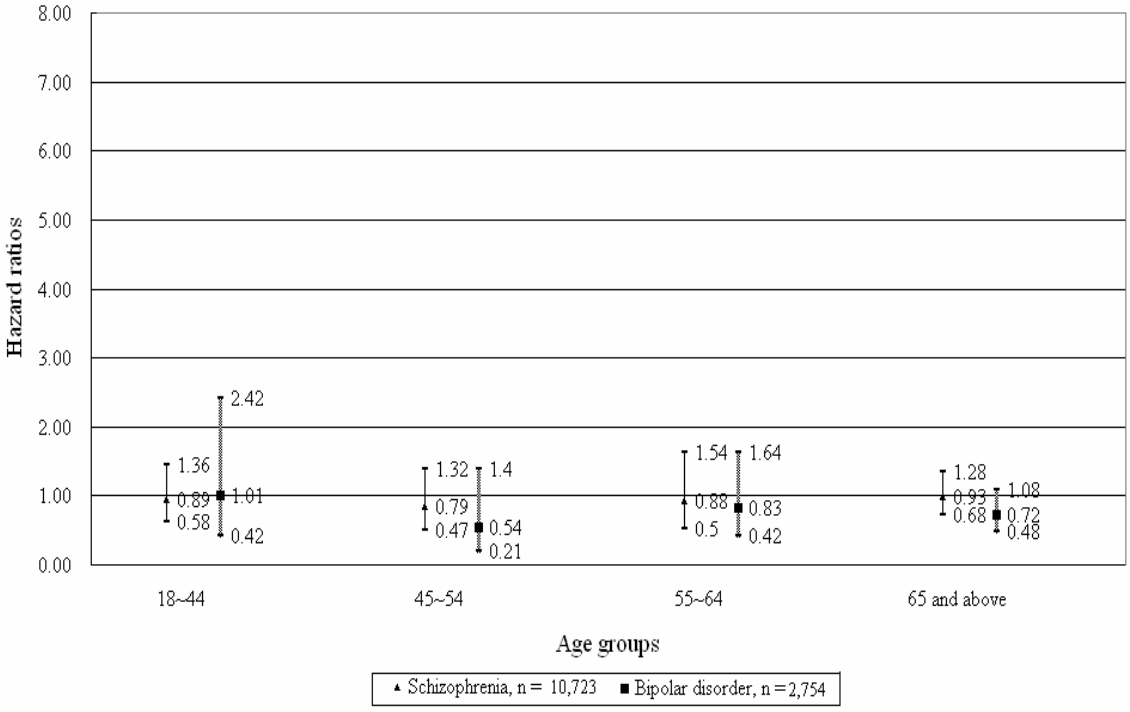
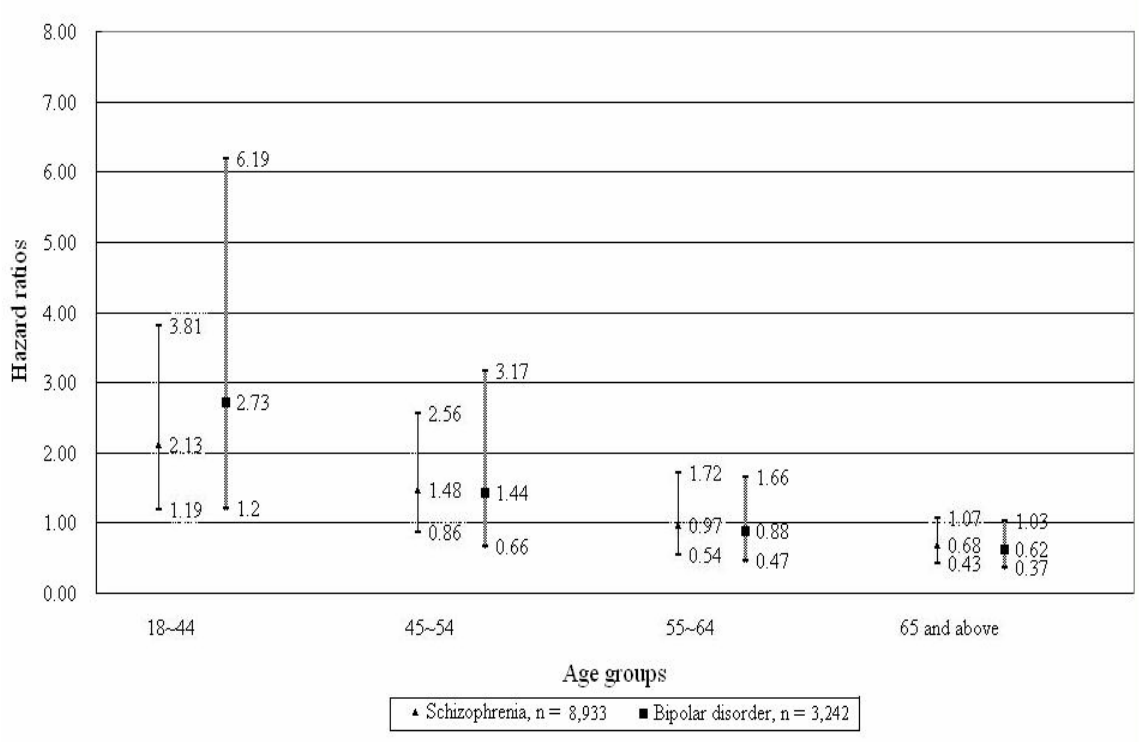


**Figure 7.3 (b) Age-stratified hazard ratios and 95% confidence intervals of AMI in women with or without schizophrenia or bipolar disorder (adjusted for age at study entry, levels of income and urbanization, cardiovascular risk factors)**




Fully adjusted results from sensitivity analyses restricted to AMI ascertained in the latter half of the surveillance period were, in essence, identical to those obtained in the analyses of the full sample (as shown in Figure **7.4 (a) and (b)**).

**Figure 7.4 (a) Sensitivity analysis restricting AMI to those ascertained in the latter half of the surveillance period: age-stratified hazard ratios and 95% confidence intervals of AMI in men with or without schizophrenia or bipolar disorder (adjusted for age at study entry, levels of income and urbanization, cardiovascular risk factors)**

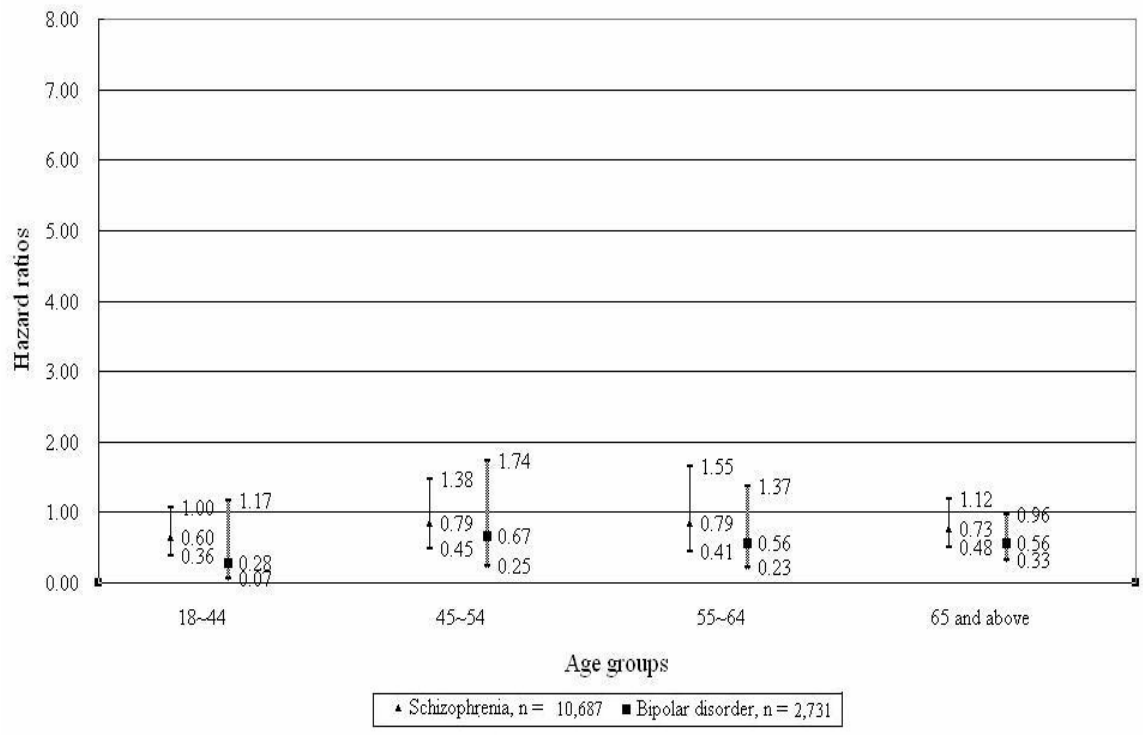
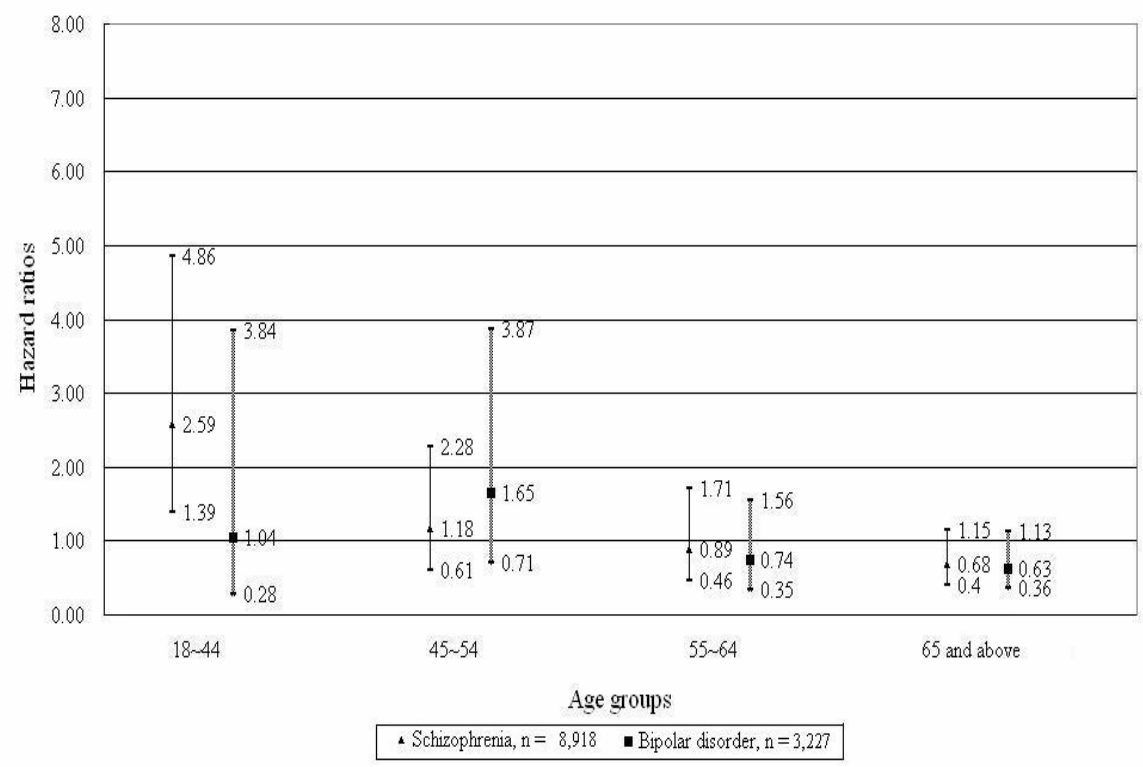


**Figure 7.4 (b) Sensitivity analysis restricting AMI to those ascertained in the latter half of the surveillance period: age-stratified hazard ratios and 95% confidence intervals of AMI in women with or without schizophrenia or bipolar disorder (adjusted for age at study entry, levels of income and urbanization, cardiovascular risk factors)**



### 7.3.5 Propensity scores calculated from logistic regression and results of Cox regression after propensity stratification

Results applying multivariate logistic regression analyses for the calculation of propensity scores using covariates listed in **Table 7.1** are shown in **Table 7.4**. The logistic regression models yielded a c-statistic of 0.93 for the validity of schizophrenia model, and 0.83 for that of bipolar disorder. These results indicated that the covariates from **Table 7.1** provided a strong ability to describe the characteristics of ‘cases’ and ‘controls’.

**Table 7.4 Multivariate logistic regression analysis for calculating propensity scores in patients with schizophrenia (R square = 0.64, c statistic = 0.93), or bipolar disorder(R square = 0.28, c statistic = 0.83), vs. control group, and covariates**

| | Schizophrenia ( n= 19,656) | | | | Bipolar disorder (n=5,996) | | | |
|---|---|---|---|---|---|---|---|---|
| Variable | Odds ratios | b | SE of b | p | Odds ratios | b | SE of b | p |
| Intercept | | -4.22 | 0.04 | <0.001 | | -5.40 | 0.06 | <0.001 |
| Age group at study entry | | | | | | | | |
| 18~34 | 1 | 0 | | | 1 | 0 | | |
| 35~44 | 0.79 | -0.23 | 0.03 | <0.001 | 1.00 | 0.004 | 0.04 | 0.91 |
| 45~54 | 0.55 | -0.60 | 0.04 | <0.001 | 0.72 | -0.33 | 0.05 | <0.001 |
| 55~64 | 0.35 | -1.05 | 0.05 | <0.001 | 0.49 | -0.72 | 0.06 | <0.001 |
| 66 and above | 0.28 | -1.26 | 0.05 | <0.001 | 0.47 | -0.75 | 0.05 | <0.001 |
| Gender | | | | | | | | |
| Men | 1.29 | 0.26 | 0.02 | <0.001 | 0.89 | 0.11 | 0.03 | 0.002 |
| Women | 1 | 0 | | | 1 | 0 | | |
| Levels of urbanization | | | | | | | | |
| 1 (most urbanized) | 1 | 0 | | | 1 | 0 | | |
| 2 | 1.13 | 0.12 | 0.03 | <0.001 | 0.96 | -0.04 | 0.04 | 0.23 |
| 3 | 1.14 | 0.13 | 0.04 | <0.001 | 0.84 | -0.18 | 0.05 | <0.001 |
| 4 | 1.29 | 0.26 | 0.04 | <0.001 | 0.96 | -0.04 | 0.05 | 0.44 |
| 5 (least urbanized) | 1.75 | 0.56 | 0.04 | <0.001 | 1.20 | 0.18 | 0.05 | <0.001 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Monthly income | | | | | | | | |
| NT 0 | 1 | 0 | | | 1 | 0 | | |
| NT$ 1~15840 | 1.53 | 0.43 | 0.03 | <0.001 | 1.21 | 0.19 | 0.42 | <0.001 |
| NT$ 15841 ~ 25000 | 0.85 | -0.17 | 0.03 | <0.001 | 0.75 | -0.28 | 0.04 | <0.001 |
| ≧NT$ 25001 | 0.34 | -1.07 | 0.05 | <0.001 | 0.66 | -0.42 | 0.05 | <0.001 |
| History of medical disorders before study entry | | | | | | | | |
| Hypertension | 0.62 | -0.48 | 0.05 | <0.001 | 2.83 | 1.04 | 0.04 | <0.001 |
| Diabetes | 1.69 | 0.52 | 0.06 | <0.001 | 3.97 | 1.38 | 0.05 | <0.001 |
| Hyperlipidemia | 0.78 | -0.25 | 0.06 | <0.001 | 2.64 | 0.97 | 0.05 | <0.001 |
| Alcohol use disorders | 4.50 | 1.50 | 0.09 | <0.001 | 59.35 | 4.08 | 0.07 | <0.001 |
| Angina | 1.99 | 0.69 | 0.07 | 0.69 | 4.57 | 1.52 | 0.05 | <0.001 |
| History of visiting psychiatric department before study entry | 126.19 | 4.84 | 0.03 | <0.001 | | | | |
| Hospital levels of visits before study entry | | | | | | | | |
| Medical centers | 1.47 | 0.38 | 0.02 | <0.001 | 4.01 | 1.39 | 0.04 | <0.001 |
| Regional hospitals | 1.81 | 0.59 | 0.03 | <0.001 | 2.89 | 1.06 | 0.03 | <0.001 |
| District hospitals | 1.19 | 0.17 | 0.03 | <0.001 | 1.59 | 0.46 | 0.04 | <0.001 |
| Primary care | 1 | 0 | | | 1 | 0 | | |

**Figure 7.5(a)** and **7.5(b)** illustrate the distribution of the propensity score (or the probability that subjects being assigned to the case group) estimated using logistic regression by covariates listed in **Table 7.1**. Patients with diagnosis of schizophrenia or bipolar disorder had significantly higher propensity score than those without psychiatric diagnosis, which indicated that patients with diagnosis of schizophrenia or bipolar disorder had significantly higher probability being assigned to the case group before propensity stratification.

Moreover, after such propensity score stratification, patient characteristics of the case and comparison groups within each propensity score stratum tended to be similar, some of the differences became insignificant ($p>0.05$) (please see **Table 7.5 (a) and (b)** for propensity stratum in which the differences of patient characteristics became insignificant). Finally, gender and entry age were stratified for Cox regression analysis.

**Figure 7.5(a) Distribution of estimated propensity scores in people with or without schizophrenia**

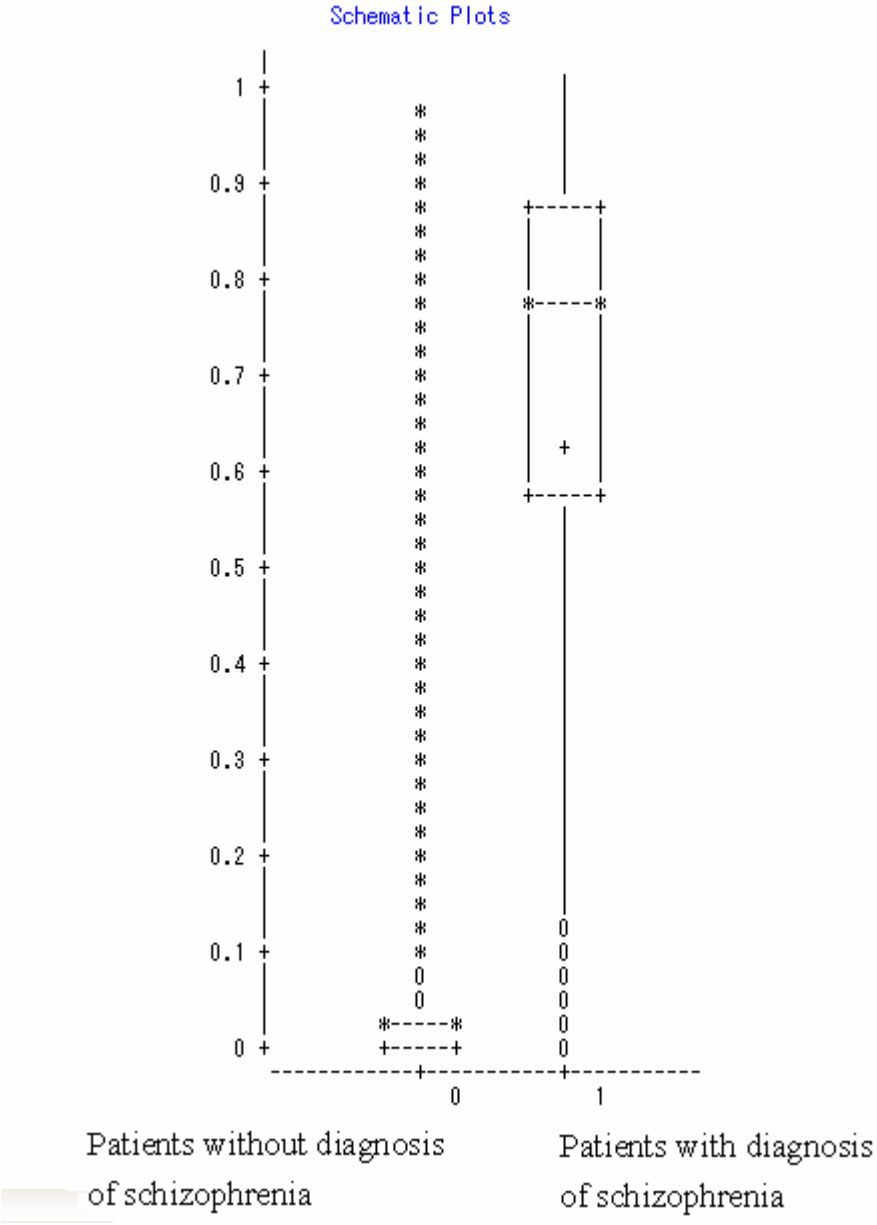


**Figure 7.5(b) Distribution of estimated propensity scores in people with or without bipolar disorder**

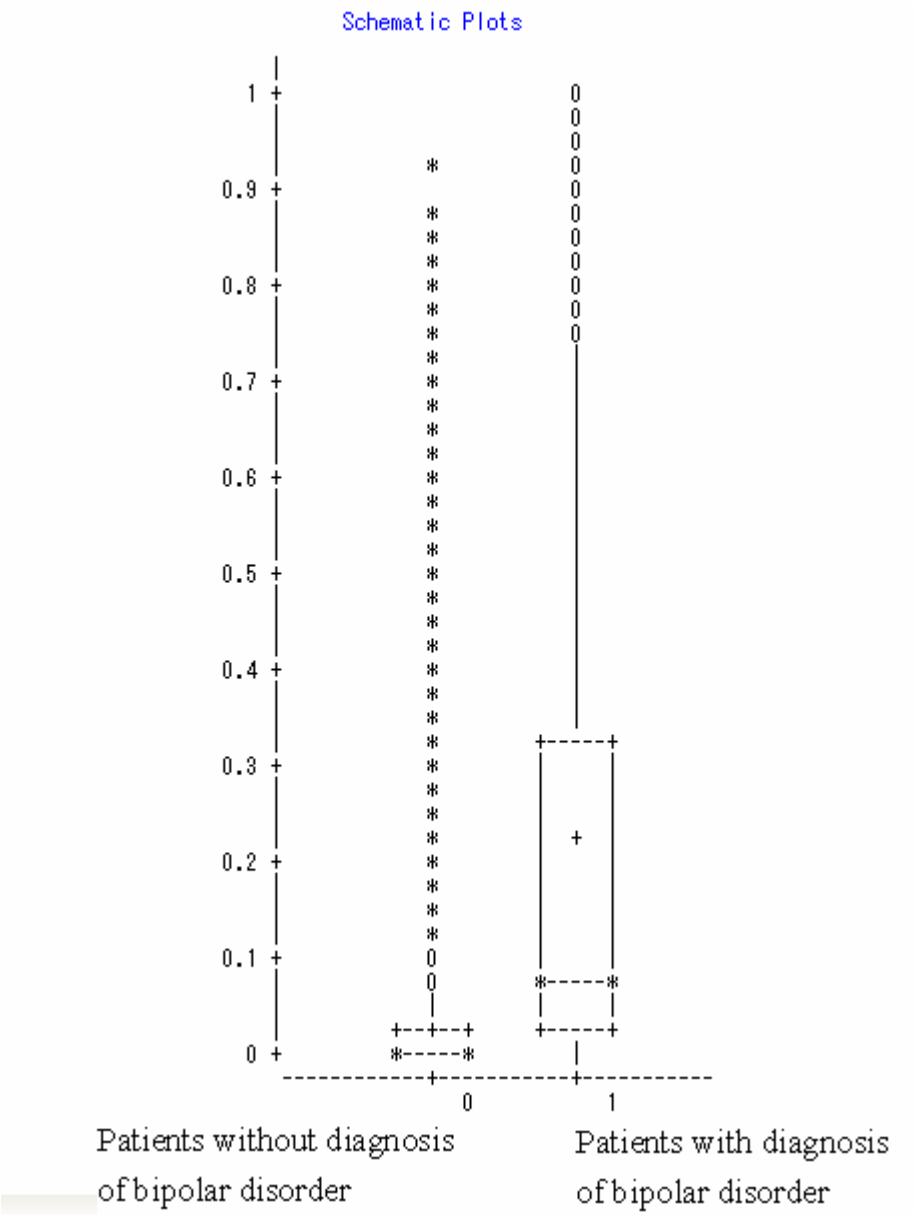


**Table 7.5(a) Stratum in which differences of patient characteristics became insignificant between people with or without schizophrenia ('case' vs. 'control') after propensity stratification**

| | No serious mental illness | Schizophrenia | Test statistic, degree of freedom (df), P value |
|---|---|---|---|
| Gender, in the strata which 'case' and 'control' had between 20th ~ 30th percentile of propensity scores (%) | | | $\chi^2$ 3.21, df 1, p=0.07 |
| Men | 39.4 | 42.9 | |
| Women | 60.6 | 57.1 | |
| Levels of urbanization, in the strata which 'case' and 'control' had between 30th ~ 40th percentile of propensity scores | | | $\chi^2$ 11.4, df 4, p=0.02 |
| 1 (most urbanized) | 30.0 | 30.3 | |
| 2 | 35.8 | 32.0 | |
| 3 | 12.3 | 16.7 | |
| 4 | 12.4 | 11.3 | |
| 5 (least urbanized) | 9.5 | 9.8 | |
| History of diabetes, in the strata which 'case' and 'control' had > 40th percentile of propensity scores (%) | | | $\chi^2$ 0.39, df 1, p=0.53 |
| | 6.4 | 6.7 | |
| History of hyperlipidemia, in the strata which 'case' and 'control' between 30th ~ 40th percentile of propensity scores (%) | | | $\chi^2$ 0.03, df 1, p=0.86 |
| | 6.2 | 6.0 | |
| History of alcohol use disorder, in the strata which 'case' and 'control' between 30th ~ 40th percentile of propensity scores (%) | | | $\chi^2$ 1.46, df 1, p=0.23 |
| | 0.0 | 0.2 | |
| History of angina, in the strata which 'case' and 'control' between 30th ~ 40th percentile of propensity scores (%) | | | $\chi^2$ 4.85, df 1, p=0.03 |
| | 7.5 | 5.4 | |
| History of angina, in the strata which 'case' and 'control' > 40th percentile of propensity scores (%) | | | $\chi^2$ 4.33, df 1, p=0.04 |
| | 3.3 | 2.5 | |
| Hospital levels of visits before study entry, in the strata which 'case' and 'control' between 30th ~ 40th percentile of propensity scores (%) | | | $\chi^2$ 4.15, df 1, p=0.04 |
| Primary care | 4.0 | 5.7 | |
| Acute myocardial infarction, in the strata which 'case' and | | | $\chi^2$ 1.48, df 1, p=0.22 |

| | | | |
|---|---|---|---|
| ‘control’ <20$^{th}$ percentile of propensity scores (%) | | | |
| | 1.1 | 1.3 | |
| Acute myocardial infarction, in the strata which ‘case’ and ‘control’ between 20$^{th}$ ~ 30$^{th}$ percentile of propensity scores (%) | | | $\chi^2$ 0.09, df 1, p=0.76 |
| | 2.0 | 1.9 | |
| Acute myocardial infarction, in the strata which ‘case’ and ‘control’ between 30$^{th}$ ~ 40$^{th}$ percentile of propensity scores (%) | | | $\chi^2$ 0.28, df 1, p=0.60 |
| | 1.6 | 1.3 | |

**Table 7.5(b) Stratum in which differences of patient characteristics became insignificant between people with or without bipolar disorder ('case' vs. 'control') after propensity stratification**

| | No serious mental illness | Bipolar disorder | Test statistic, degree of freedom (df), P value |
|---|---|---|---|
| Age group at study entry, in the strata which 'case' and 'control' had between 20th ~ 30th percentile of propensity scores (%) | | | $\chi^2$ 1.76, df 3, p=0.62 |
| 18~44 | 50.2 | 48.0 | |
| 45~54 | 15.9 | 15.6 | |
| 55~64 | 15.1 | 16.1 | |
| >64 years | 18.7 | 20.3 | |
| Age group at study entry, in the strata which 'case' and 'control' had between 30th ~ 40th percentile of propensity scores (%) | | | $\chi^2$ 2.62, df 3, p=0.45 |
| 18~44 | 49.6 | 50.8 | |
| 45~54 | 25.4 | 27.0 | |
| 55~64 | 9.8 | 8.9 | |
| >64 years | 15.2 | 13.3 | |
| Gender, in the strata which 'case' and 'control' had between 20th ~ 30th percentile of propensity scores (%) | | | $\chi^2$ 0.71, df 1, p=0.40 |
| Men | 44.8 | 46.6 | |
| Women | 55.2 | 53.4 | |
| Gender, in the strata which 'case' and 'control' had between 30th ~ 40th percentile of propensity scores (%) | | | $\chi^2$ 0.80, df 1, p=0.06 |
| Men | 40.6 | 40.1 | |
| Women | 59.42 | 59.9 | |
| Levels of income, in the strata which 'case' and 'control' had between 20th ~ 30th percentile of propensity scores | | | $\chi^2$ 0.18, df 3, p=0.98 |
| NT 0 | 26.3 | 25.7 | |
| NT$ 1~15840 | 28.7 | 28.7 | |
| NT$ 15841 ~ 25000 | 30.4 | 31.2 | |
| ≧NT$ 25001 | 14.6 | 14.4 | |
| Levels of income, in the strata which 'case' and 'control' had between 30th ~ 40th percentile of propensity scores | | | $\chi^2$ 0.93, df 3, p=0.82 |
| NT 0 | 27.5 | 28.6 | |
| NT$ 1~15840 | 13.3 | 12.6 | |

| | | | |
|---|---|---|---|
| NT$ 15841 ~ 25000 | 37.1 | 37.8 | |
| ≧NT$ 25001 | 22.2 | 21.0 | |
| Levels of urbanization, in the strata which 'case' and 'control' had between 20th ~ 30th percentile of propensity scores | | | $\chi^2$ 2.39, df 4, p=0.66 |
| 1 (most urbanized) | 31.9 | 33.6 | |
| 2 | 28.8 | 29.3 | |
| 3 | 15.0 | 15.4 | |
| 4 | 12.1 | 10.8 | |
| 5 (least urbanized) | 12.2 | 10.8 | |
| Levels of urbanization, in the strata which 'case' and 'control' had between 30th ~ 40th percentile of propensity scores | | | $\chi^2$ 2.57, df 4, p=0.63 |
| 1 (most urbanized) | 37.7 | 37.4 | |
| 2 | 26.1 | 27.7 | |
| 3 | 17.3 | 18.1 | |
| 4 | 10.8 | 8.9 | |
| 5 (least urbanized) | 8.1 | 8.0 | |
| Levels of urbanization, in the strata which 'case' and 'control' had > 40th percentile of propensity scores | | | $\chi^2$ 5.82, df 4, p=0.21 |
| 1 (most urbanized) | 36.2 | 34.2 | |
| 2 | 29.9 | 30.5 | |
| 3 | 11.9 | 12.3 | |
| 4 | 11.9 | 12.0 | |
| 5 (least urbanized) | 10.2 | 10.9 | |
| History of hypertension, in the strata which 'case' and 'control' had < 20th percentile of propensity scores (%) | | | $\chi^2$ 0.08, df 1, p=0.78 |
| | 2.5 | 2.7 | |
| History of hypertension, in the strata which 'case' and 'control' had between 30th ~ 40th percentile of propensity scores (%) | | | $\chi^2$ 3.62, df 1, p=0.06 |
| | 11.1 | 8.6 | |
| History of diabetes, in the strata which 'case' and 'control' had between 20th ~ 30th percentile of propensity scores (%) | | | $\chi^2$ 0.22, df 1, p=0.64 |
| | 3.1 | 2.8 | |
| History of diabetes, in the strata which 'case' and 'control' had between 30th ~ 40th percentile of propensity scores (%) | | | $\chi^2$ 3.18, df 1, p=0.08 |
| | 4.3 | 2.8 | |
| History of hyperlipidemia, in the strata which 'case' and 'control' had < 20th percentile of propensity scores (%) | | | $\chi^2$ 2.91, df 1, p=0.09 |
| | 0.8 | 0.3 | |

| | | | |
|---|---|---|---|
| History of hyperlipidemia, in the strata which 'case' and 'control' had between $20^{th} \sim 30^{th}$ percentile of propensity scores (%) | | | $\chi^2$ 3.20, df 1, p=0.07 |
| | 4.9 | 3.3 | |
| History of angina, in the strata which 'case' and 'control' between $20^{th} \sim 30^{th}$ percentile of propensity scores (%) | | | $\chi^2$ 3.91, df 1, p=0.05 |
| | 1.9 | 0.8 | |
| Hospital levels of visits before study entry, in the strata which 'case' and 'control' had between $30^{th} \sim 40^{th}$ percentile of propensity scores (%) | | | $\chi^2$ 1.00, df 1, p=0.32 |
| District hospital | 70.6 | 72.5 | |
| Hospital levels of visits before study entry, in the strata which 'case' and 'control' had between $20^{th} \sim 30^{th}$ percentile of propensity scores (%) | | | $\chi^2$ 0.54, df 1, p=0.46 |
| Primary care | 97.9 | 98.4 | |
| Hospital levels of visits before study entry, in the strata which 'case' and 'control' had between $30^{th} \sim 40^{th}$ percentile of propensity scores (%) | | | $\chi^2$ 0.994, df 1, p=0.33 |
| Primary care | 98.3 | 98.8 | |
| Hospital levels of visits before study entry, in the strata which 'case' and 'control' > $40^{th}$ percentile of propensity scores (%) | | | $\chi^2$ 0.0002, df 1, p=0.99 |
| Primary care | 98.7 | 98.7 | |
| Acute myocardial infarction, in the strata which 'case' and 'control' had between $20^{th} \sim 30^{th}$ percentile of propensity scores (%) | | | $\chi^2$ 0.0001, df 1, p=0.99 |
| | 1.5 | 1.5 | |
| Acute myocardial infarction, in the strata which 'case' and 'control' between $30^{th} \sim 40^{th}$ percentile of propensity scores (%) | | | $\chi^2$ 2.75, df 1, p=0.10 |
| | 1.3 | 2.2 | |
| Acute myocardial infarction, in the strata which 'case' and 'control' between $30^{th} \sim 40^{th}$ percentile of propensity scores (%) | | | $\chi^2$ 1.37, df 1, p=0.24 |
| | 2.2 | 1.9 | |

Results from adjusted Cox regression models after propensity stratification are summarized in **Table 7.6**. Similar to the main analysis, addition of history of coronary artery diseases, hypertension, diabetes and hyperlipidaemia to the models substantially attenuated the hazard ratios for both serious mental illnesses. **Figures 7.6 (a)** and **(b)** summarize the fully adjusted age and gender stratified models for schizophrenia and bipolar disorder after propensity stratification. It was observed that risks of AMI in the two case cohorts were raised in two younger age groups for women, but were more equivocal for men. Gender x disorder, age group x disorder, and three-way (age group x gender x disorder) interaction terms were tested in fully adjusted models and were not found to be significant (p-values >0.10) in people with or without schizophrenia. However, age-modification was found in the fully adjusted model in people with bipolar disorder with the older age x disorder interaction term of 0.76 (95% CI 0.63~0.91, p=0.003). In addition, although no gender interaction was found (interaction term 0.68, 95% CI 0.46~1.02, p=0.06), three-way (age group x gender x disorder) interaction was found to be significant in people with bipolar disorder in the fully adjusted model (interaction term 0.93, 95% CI 0.88~0.99, p=0.02).

Considering independent influences on the AMI outcome, the strongest associations in final models were for cardiovascular risk factors in schizophrenia (i.e. coronary artery diseases: HR 2.29 (95% CI 1.92~2.73), p<0.001; hypertension: HR 1.63 (95% CI 1.43~1.85), p<0.001). Similarly, associations for cardiovascular risk factors in bipolar disorder were: coronary artery diseases: HR 1.95 (95% CI 1.58~2.40), p<0.001 and hypertension: HR 1.46 (95% CI 1.25~1.69), p<0.001).

On testing interactions with age, there were significant negative terms for women with schizophrenia (HR: 0.96 (95% CI 0.94~0.99, p=0.001) and bipolar disorder (HR:

0.97 (95% CI 0.95~1.00, p=0.02), indicating a stronger excess risk in younger women with this disorder.

**Table 7.6 (a) Additional analysis: Hazard ratios (HR) of AMI in people with and without schizophrenia after propensity stratification**

| | Unadjusted HR | Model 1 | Model 2 | Model 3 |
|---|---|---|---|---|
| Male (Age groups ) | | | | |
| Total male | 1.00 ( 0.76 ~ 1.32 ) | 0.94 ( 0.71 ~ 1.24 ) | 0.91 ( 0.69 ~ 1.20 ) | 0.88 ( 0.66 ~ 1.18 ) |
| 18~44 | 1.10 ( 0.57 ~ 2.12 ) | 0.91 ( 0.47 ~ 1.76 ) | 0.88 ( 0.45 ~ 1.71 ) | 0.88 ( 0.45 ~ 1.72 ) |
| 45~54 | 0.88 ( 0.45 ~ 1.71 ) | 0.81 ( 0.41 ~ 1.58 ) | 0.78 ( 0.40 ~ 1.54 ) | 0.76 ( 0.38 ~ 1.53 ) |
| 55~64 | 1.03 ( 0.49 ~ 2.19 ) | 1.01 ( 0.48 ~ 2.15 ) | 0.97 ( 0.46 ~ 2.05 ) | 0.96 ( 0.43 ~ 2.12 ) |
| 65 and above | 0.95 ( 0.63 ~ 1.41 ) | 1.02 ( 0.69 ~ 1.52 ) | 1.00 ( 0.67 ~ 1.49 ) | 0.96 ( 0.64 ~ 1.45 ) |
| Female (Age groups) | | | | |
| Total female | 1.34 ( 0.95 ~ 1.88 ) | 1.11 ( 0.79 ~ 1.54 ) | 1.11 ( 0.80 ~ 1.55 ) | 1.07 ( 0.75 ~ 1.52 ) |
| 18~44 | **2.88 ( 1.20 ~ 6.89 )** | **2.49 ( 1.03 ~ 5.99 )** | **2.48 ( 1.04 ~ 6.89 )** | **2.72 ( 1.14 ~ 6.50 )** |
| 45~54 | 1.67 ( 0.79 ~ 3.51) | 1.57 ( 0.75 ~ 3.32) | 1.59 ( 0.75 ~ 3.38) | 1.53 ( 0.66 ~ 3.54) |
| 55~64 | 1.08 ( 0.54 ~ 2.15 ) | 1.03 ( 0.52 ~ 2.06 ) | 1.06 ( 0.54 ~ 2.10 ) | 1.13 ( 0.55 ~ 2.32 ) |
| 65 and above | 0.95 ( 0.55 ~ 1.64 ) | 0.86 ( 0.51 ~ 1.47 ) | 0.85 ( 0.50 ~ 1.45 ) | 0.78 ( 0.45 ~ 1.36 ) |
| All (Age groups) | | | | |
| Total | 1.12 ( 0.90 ~ 1.38 ) | 0.99 ( 0.80 ~ 1.22 ) | 0.98 ( 0.79 ~ 1.21 ) | 0.94 ( 0.75 ~ 1.17 ) |
| 18~44 | 1.43 ( 0.85 ~ 2.38 ) | 1.19 ( 0.70 ~ 2.02 ) | 1.16 ( 0.68 ~ 1.97 ) | 1.16 ( 0.68 ~ 2.00 ) |
| 45~54 | 1.09 ( 0.67 ~ 1.78 ) | 1.06 ( 0.65 ~ 1.74 ) | 1.03 ( 0.63 ~ 1.70 ) | 0.99 ( 0.58 ~ 1.67 ) |
| 55~64 | 1.05 ( 0.64 ~ 1.73 ) | 1.03 ( 0.62 ~ 1.70 ) | 0.98 ( 0.59 ~ 1.62 ) | 1.00 ( 0.59 ~ 1.70 ) |

| | | | | |
|---|---|---|---|---|
| 65 and above | 0.95 ( 0.69 ~ 1.31 ) | 0.95 ( 0.69 ~ 1.31 ) | 0.99 ( 0.65 ~ 1.51 ) | 0.89 ( 0.64 ~ 1.23 ) |

Model 1: stratified by propensity score levels and adjusted for age at study entry
Model 2: stratified by propensity score levels and adjusted for gender (where not stratified), age at study entry, levels of income, levels of urbanization, and hospital levels before study entry
Model 3: stratified by propensity score levels and adjusted for gender (where not stratified), age at study entry, levels of income, levels of urbanization, previous coronary heart disease hypertension, diabetes, and hyperlipidaemia

**Table 7.6 (b) Additional analysis: Hazard ratios (HR) of AMI in people with and without bipolar disorder after propensity stratification**

| | Unadjusted HR | Model 1 | Model 2 | Model 3 |
|---|---|---|---|---|
| Male (Age groups ) | | | | |
| Total male | 0.80 ( 0.60 ~ 1.06 ) | 0.83 ( 0.62 ~ 1.09 ) | 0.81 ( 0.62 ~ 1.08 ) | **0.69 ( 0.52 ~ 0.92 )** |
| 18~44 | 1.13 ( 0.56 ~ 2.30 ) | 1.11 ( 0.55 ~ 2.25 ) | 1.16 ( 0.57 ~ 2.36 ) | 1.01 ( 0.49 ~ 2.09 ) |
| 45~54 | 0.67 ( 0.29 ~ 1.53 ) | 0.63 ( 0.27 ~ 1.45 ) | 0.64 ( 0.28 ~ 1.46 ) | 0.51 ( 0.22 ~ 1.21 ) |
| 55~64 | 0.97 ( 0.52 ~ 1.81 ) | 0.95 ( 0.51 ~ 1.76 ) | 0.91 ( 0.50 ~ 1.70 ) | 0.74 ( 0.39 ~ 1.43 ) |
| 65 and above | 0.76 ( 0.52 ~ 1.12 ) | 0.82 ( 0.56 ~ 1.21 ) | 0.81 ( 0.55 ~ 1.19 ) | 0.73 ( 0.49 ~ 1.09 ) |
| Female (Age groups) | | | | |
| Total female | **1.36 ( 1.02 ~ 1.82 )** | 1.23 ( 0.92 ~ 1.64 ) | 1.23 ( 0.92 ~ 1.64 ) | 0.92 ( 0.67 ~ 1.26 ) |
| 18~44 | **3.52 ( 1.67 ~ 7.40 )** | **3.44 ( 1.63 ~ 7.22 )** | **3.35 ( 1.60 ~ 7.04 )** | 2.21 ( 0.95 ~ 5.13 ) |
| 45~54 | 1.91 ( 0.94 ~ 3.88) | 1.87 ( 0.92 ~ 3.80) | 1.91 ( 0.93 ~ 3.91) | 1.43 ( 0.65 ~ 3.19 ) |
| 55~64 | 1.53 ( 0.86 ~ 2.64 ) | 1.48 ( 0.86 ~ 2.55 ) | 1.46 ( 0.85 ~ 2.51 ) | 0.93 ( 0.50 ~ 1.72 ) |
| 65 and above | 0.87 ( 0.54 ~ 1.40 ) | 0.79 ( 0.49 ~ 1.27 ) | 0.79 ( 0.49 ~ 1.28 ) | 0.65 ( 0.39 ~ 1.09 ) |
| All (Age groups) | | | | |
| Total | 1.03 ( 0.84 ~ 1.25 ) | 1.00 ( 0.82 ~ 1.22 ) | 0.98 ( 0.80 ~ 1.20 ) | **0.77 ( 0.62 ~ 0.95 )** |
| 18~44 | **1.99 ( 1.20 ~ 3.30)** | **1.92 ( 1.16 ~ 3.17)** | **1.93 ( 1.17 ~ 3.20)** | 1.38 ( 0.80 ~ 2.39) |
| 45~54 | 1.12 ( 0.65 ~ 1.90 ) | 1.07 ( 0.63 ~ 1.83 ) | 1.10 ( 0.65 ~ 1.88 ) | 0.69 ( 0.39 ~ 1.24 ) |
| 55~64 | 1.24 ( 0.83 ~ 1.87 ) | 1.21 ( 0.80 ~ 1.81 ) | 1.20 ( 0.80 ~ 1.80 ) | 0.83 ( 0.53 ~ 1.30 ) |

| | | | | |
|---|---|---|---|---|
| 65 and above | 0.81 ( 0.60 ~ 1.10 ) | 0.81 ( 0.60 ~ 1.10 ) | 0.81 ( 0.60 ~ 1.09 ) | **0.69 ( 0.51 ~ 0.95 )** |

Model 1: stratified by propensity score levels and adjusted for age at study entry
Model 2: stratified by propensity score levels and adjusted for gender (where not stratified), age at study entry, levels of income, levels of urbanization, and hospital levels before study entry
Model 3: stratified by propensity score levels and adjusted for gender (where not stratified), age at study entry, levels of income, levels of urbanization, previous coronary heart disease hypertension, diabetes, and hyperlipidaemia

**Figure 7.6 (a) Additional analysis: Age-stratified hazard ratios and 95% confidence intervals of AMI in men with or without schizophrenia or bipolar disorder (stratified by propensity score levels and adjusted for age at study entry, levels of income, levels of urbanization, previous coronary heart disease hypertension, diabetes, hyperlipidaemia, and alcohol use disorders)**

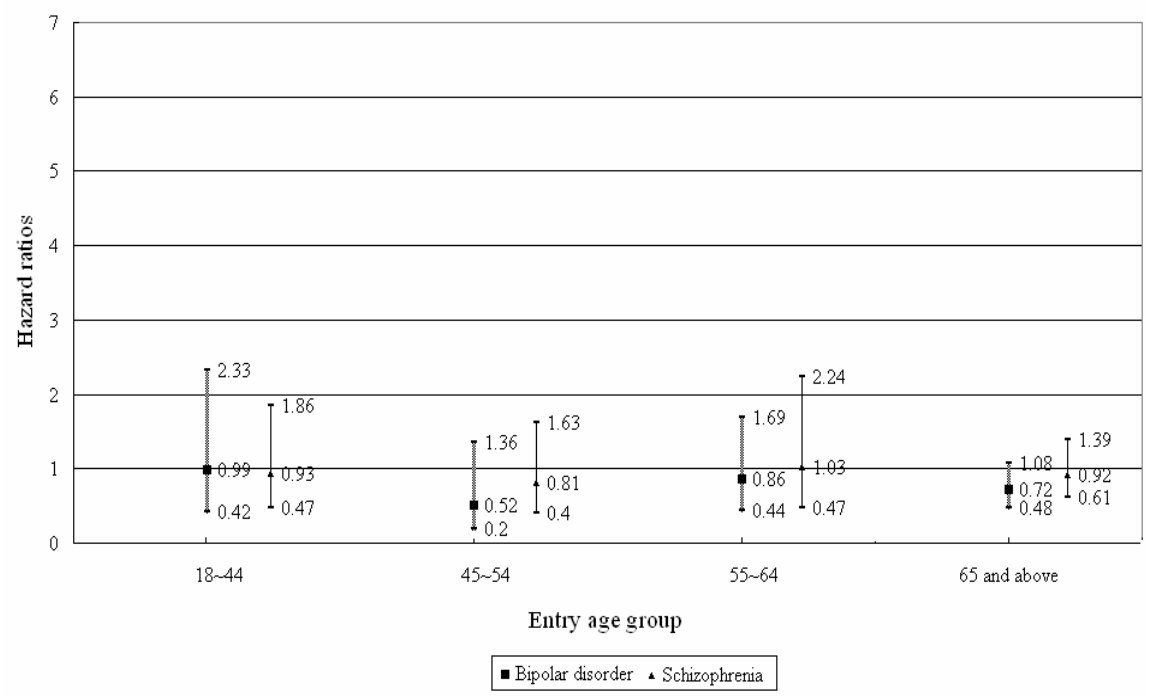
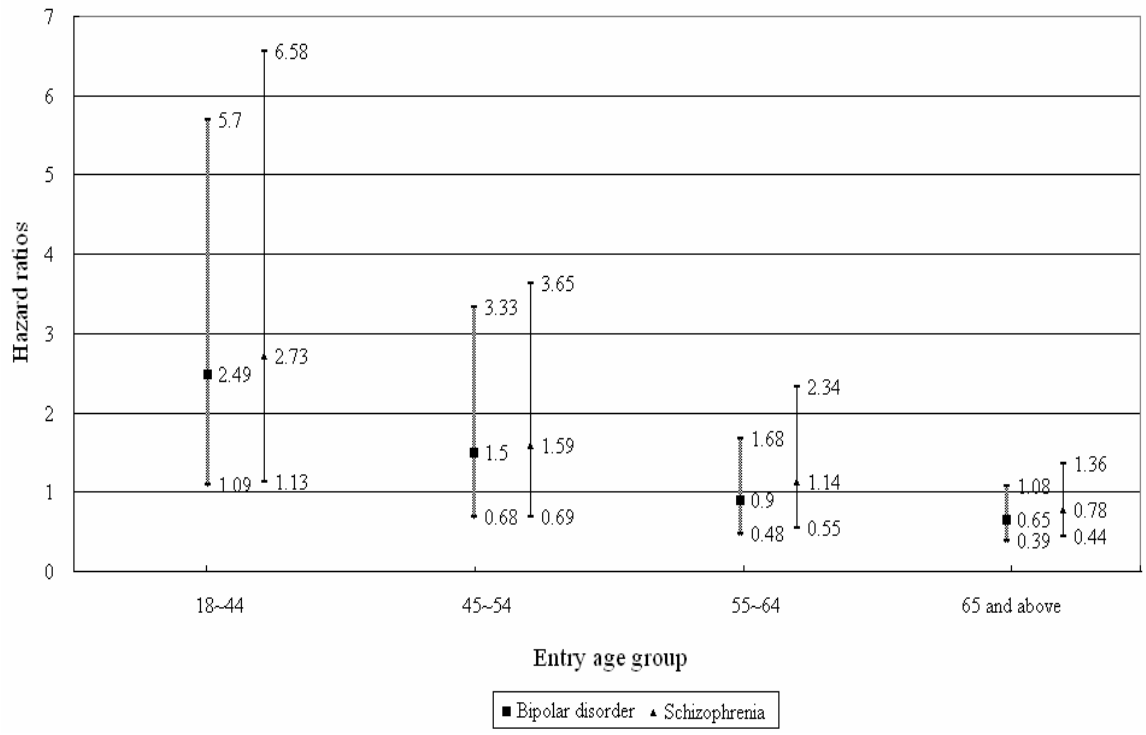


**Figure 7.6 (b) Additional analysis: Age-stratified hazard ratios and 95% confidence intervals of AMI in <u>women</u> with or without schizophrenia or bipolar disorder (stratified by propensity score levels and adjusted for age at study entry, levels of income, levels of urbanization, previous coronary heart disease hypertension, diabetes, hyperlipidaemia, and alcohol use disorders)**



## 7.4 Discussion

### 7.4.1 Summary

In this large analysis of national health care records, schizophrenia was not associated with increased risk of AMI in the total sample or in most sub-groups. Bipolar disorder was associated with increased risk of AMI following adjustment for sociodemographic factors but with lower risk of AMI when further adjusted for cardiovascular risk factors. One sub-group of young women (below 45 years) with schizophrenia and bipolar disorder were found to have a significantly increased risk of AMI over a 12-year surveillance period than counterparts without SMI. Results did not change substantially after propensity stratification, although bipolar disorder was primarily associated with either no change or decreased AMI risk following this method of adjustment.

### 7.4.2 No significant association between schizophrenia and risk of AMI

This investigation of the risk of AMI in people with SMI was carried out on the largest database of psychiatric inpatients to date, comparing these with a nationally representative sample of comparison cohort. Although there was some evidence of isolated excess risk in younger women, contrary to the study hypothesis no increased risk of AMI was found in people with schizophrenia for the sample overall. This null finding is consistent with some studies (Curkendall et al., 2004; Laursen et al., 2011; Lin et al., 2008; Truyers et al., 2011) but is not in line with other positive associations summarised in **Chapter 2**. One possible explanation is that the sample with SMI in this cohort were more severely affected by their psychotic disorder, so that those who survived into mid- and late-life were healthier in other ways. Also, other non-AMI causes of death might be responsible for the recognised excess mortality in people with SMI in Taiwan (Chen WJ et al., 1996; Chen YH et al., 2010) resulting in further selection bias through survival (Truyers et al., 2011). In addition,

it is important to bear in mind that there might be over-adjustment resulting in an obscured association in fully adjusted models (Model 3), since cardiovascular risk factors (hyperlipidaemia, hypertension, diabetes) may lie on the causal pathway between mental disorder and AMI risk.

A further reason might be that the Taiwanese population is relatively protected with respect to cardiovascular outcomes compared to populations in Western countries. Although the incidence rate of AMI in Taiwan rose from 51 to 108 per 100,000 population per year in men and 27 to 50 per 100,000 population per year in women from year 1996 to 2007 (Department of Health in Taiwan, 2008; Peng, 2009), these figures remain lower than those from the UK, where the incidence rate declined from 230 to 154 per 100,000 population per year in men and 95 to 66 per 100,000 population per year in women from year 2002 to 2007 (Birkhead J, 1999; Smolina K, 2012). Better cardiovascular risk profiles have also been reported in the Taiwanese population (prevalence of hypertension ranging from 13~21%; dyslipidemia: 6~20%; hyperglycemia: 7~8%; and overweight: 24~38%)(Bureau of Health Promotion, Department of Health in Taiwan, 2008) than that in European countries (prevalence of hypertension ranging from 35~48%; dyslipidemia: 27~70%; hyperglycemia: 5~12%; and overweight: 24~63%)(Nichols M, 2012). Hence, it is possible that the disparities of cardiovascular risk profiles and incidence of AMI between people with or without SMI are not as large as those in Western settings.

Another explanation to bear in mind is the possibility of under-detection of AMI in people with SMI (Laursen et al., 2011), particularly when the diagnosis of AMI could only be ascertained from these administrative data recorded by treating physicians for claim purposes. That is, in order for the diagnosis of AMI to be given, patients must have had medical contacts and sought medical help. Patients with mental

disorders have been reported to be a group that experiences barriers to seeking medical help compared with the general population (Felker et al., 1996). Previous research has reported possible insufficient physical or laboratory examinations required for the ascertainment of AMI, and under-referral for relevant treatment (Laursen et al., 2011). Underlying causes for difficulty accessing medical care in people with SMI cited by previous research have included lack of communication skills (Worley et al., 1990), refusal of recommended consultations (Kampmeier, 1977; McConnell et al., 1992), and physicians' negative reactions (Groves, 1978), none of which could be investigated in this particular dataset.

In addition, it should also be borne in mind that patients with negative symptoms, and those who had never presented to hospital for psychiatric treatment might be missed in the analysis. This may be relevant if these missing people lived a more unhealthy lifestyle associated with higher cardiovascular risk, such as through smoking, obesity and physical inactivity, secondary to negative symptoms of social withdrawal and self-neglect. Given the elevated standardized mortality ratios (ranging from 3.7~7.6) in deaths due to cardiovascular diseases for SMI in Taiwan (Chen WJ et al., 1996), comparable to those in Western countries (SMR: 2.1~6.0) (Kamara et al., 1998; Osby et al., 2001; Osby et al., 2000; Rasanen et al., 2003; Valenti et al., 1997), the possibility of under-recognition should be considered (Chen WJ et al., 1996) and further research is required.

### 7.4.3 Elevated risk of AMI in women with SMI, younger than 45 years of age

Despite the overall null association between the risk of AMI in people with SMI, this investigation revealed that the risk of AMI was significantly modified by age in people with schizophrenia and bipolar disorder. The age modification was still prominent after propensity stratification in people with bipolar disorder. More

specifically, in contrast to the recognised higher risk of coronary artery disease in men compared with women in premenopausal age ranges observed in most community populations, the cardioprotective effect in younger women was apparently attenuated in people with SMI. This is the first study to report age and gender modification of the risk of AMI in people with bipolar disorder; and is in agreement with another study of people with schizophrenia reporting elevated risk of cardiovascular disease in women under age 59 (Bresee et al., 2010). A large component of the reduced risk of coronary artery disease in premenopausal women is thought to be derived from a relatively favourable lipid profile with higher levels of high-density lipoprotein cholesterol (Bergemann et al., 2005). However, studies have suggested that people with schizophrenia may live with an unhealthy lifestyle from an early age (Allison et al., 1999), with predisposition to higher levels of intra-abdominal or visceral fat (Thakore et al., 2002) or higher susceptibility to poor glycaemic control (Bellivier, 2005) before any initiation of psychotropic medication. Besides, schizophrenia is a chronic disorder with up to 50% of those affected receiving long-term treatment with atypical antipsychotics (Newcomer, 2005), and a larger volume of research has suggested that the well-recognized side effects of weight gain or metabolic syndrome associated with these drugs should be of concern (Bobes et al., 2010; Newcomer, 2005). In people with SMI receiving long-term antipsychotic treatment, elevation in body weight or visceral adiposity might increase the risk of cardiovascular diseases through changes in insulin resistance (Newcomer et al., 2002), levels of triglycerides and cholesterol profiles (Meyer & Koro, 2004) or blood pressure (Newcomer, 2005). It is therefore important to establish mechanisms underlying the apparent negation of this protective effect (Bresee et al., 2010), perhaps through metabolic syndrome, cigarette smoking, lack of exercise, or decreased levels of estradiol as indicated in previous research (Bresee et al., 2010; Fountoulakis et al., 2010; Pilote et al., 2007).

### 7.4.4 Risk of AMI in patients with bipolar disorder

Relatively little research has investigated the risk of AMI in people with bipolar disorder. Previous studies have examined such associations either cross-sectionally (Kilbourne et al., 2004), or longitudinally but with smaller numbers of bipolar patients (Callaghan et al., 2009; Lin et al., 2008), and none to date have compared AMI risk and its correlates between bipolar disorder and schizophrenia. In this study, a risk effect was observed in the total sample of people with bipolar disorder that was independent of socio-demographic factors in the conventional Cox model. However, the excess risk was attenuated in the propensity stratification model, and reversed in both models once cardiovascular risk factors were included as covariates. These findings were different from those in schizophrenia where the associations were mostly null. The findings would be consistent with a risk effect of bipolar disorder on AMI which was largely mediated by worse cardiovascular risk profile; however this conclusion can only be tentative, because temporal relationships between bipolar disorder and cardiovascular risk factors could not be determined within the short follow-up period (although, given the typical ages of onset, bipolar disorder is more likely to precede cardiovascular risk factors). Considering the reversal in the direction of association in the fully adjusted model, it was possible that the diagnosis of bipolar disorder conferred some protection after taking all other factors into account, possibly because of higher levels of medical contact and recognition of risk factors. Alternatively, the findings might reflect the survival bias discussed previously. Of note, regarding potential differences in causal pathways between the two disorders, it has been suggested that behavioral or adverse physiological changes (such as increased platelet aggregation and decreased heart rate variability) during depressive or manic episodes (Katon, 2003; Kilbourne et al., 2007) might mediate at least some of the association with increased risk of cardiovascular diseases in young

women with bipolar disorder. Finally, although the association between AMI and bipolar disorder was attenuated when AMI early in the observation period was excluded, this was unlikely to be accounted for by effects of previous AMI episodes because these are likely to be rare, and may simply reflect loss of statistical power.

### 7.4.5 Strengths and limitations

Strengths of this study include the very large prospective dataset drawn from a national sample with sufficient statistical power to estimate the associations of interest with a high level of precision. Also relevant is the fact that this dataset comes from a near-universal healthcare provision system, and so can be reasonably claimed to be nationally representative. A key limitation is that findings were drawn from administrative rather than research datasets – in particular, the diagnoses were clinician-initiated and do not necessarily generalize to research diagnostic criteria, and there might be potential under reporting of true cases of AMI and mental disorders. For this reason diagnostic groups were deliberately chosen which were relatively broad and unambiguous. There were also compensating advantages in the higher generalisability of clinical (rather than research) diagnoses to naturalistic clinical environments. However, misclassification of case and comparison groups should be considered as probable to some extent. In terms of exposure, it is important to bear in mind that the case cohorts predominantly represented relatively severely affected subgroups of people with schizophrenia or bipolar disorder since the majority had been hospitalized and there were insufficient numbers of individuals drawn from the LHID2000 dataset alone (i.e. those without hospitalization) to analyze separately. This issue is particularly pertinent for bipolar disorder where a smaller proportion of LHID2000 subjects appeared on the PIMC dataset compared to schizophrenia.

Considering the outcome, it is important to bear in mind that this refers to incident hospitalizations with AMI as a primary clinical diagnosis. Evidence from electrocardiography and cardiac enzymes would be required for this according to standard clinical practice in Taiwan; however, the outcome does not capture sudden cardiac deaths outside hospital or instances of AMI which did not result in hospitalization (however, it would include instances of AMI resulting in early inpatient mortality if sufficient prior investigations had been carried out to ascertain AMI as the cause of this). A further limitation is that there was no information on lifetime history of mental disorders and cases could only be ascertained on the basis of medical contact during the follow-up window. Measurement errors in both exposure and outcome ascertainments will have obscured rather than exaggerated the associations of interest and therefore should be considered as potential explanations for associations which were expected but not found.

Considering confounding, although it was possible to adjust for demographic status and certain medical disorders, information was not available on other determinants of vascular risk status such as smoking and exercise habits, blood pressure levels, obesity or body size. These are therefore left as potential causal pathways between exposure and outcome on which it is not possible to comment. However, similar to Western studies where greater prevalence of cigarette smoking, obesity, and physical inactivity were found in people with SMI (Brown, 2000; Robson, 2007; Vancampfort, 2012), epidemiological studies in Taiwan have also reported a higher prevalence of current cigarette smoking in 70.9% of male and 11.5% of female inpatients with schizophrenia (Liao et al., 2002), compared to 46.8% of men and 4.3% of women in the general population in Taiwan (Wen et al., 2001), and a 2.51~2.74 fold higher prevalence of obesity in outpatients with schizophrenia receiving antipsychotic compared to Taiwanese reference population (Hsiao, 2004). Thus, the effect of

smoking, obesity, and physical inactivity on the increased risk of developing AMI in SMI requires consideration, particularly given findings such as the fall in the prevalence of cigarette smoking in the Scottish general population accounting for a 36% decrease in cardiovascular mortality between 1975 and 1994 (Capewell et al., 1999). In contrast, the prevalence of smoking and cardiovascular mortality was not found to have fallen in people with schizophrenia in the UK (Brown, 2010; The Information Centre, 2006), emphasizing that reducing cigarette smoking in people with SMI might still be the most important prevention strategy for cardiovascular morbidity and mortality (Capewell et al., 1999; Brown, 2010).

# CHAPTER 8

# DIAGNOSTIC PROCEDURES, REVASCULARIZATION, AND INPATIENT MORTALITY AFTER ACUTE MYOCARDIAL INFARCTION IN PATIENTS WITH SCHIZOPHRENIA AND BIPOLAR DISORDER

## 8.1 Objective

To investigate, within a system that has tried to eliminate economic barriers to healthcare, the equality of intervention receipts, outcome of inpatient mortality or recurrence following the first acute myocardial infarction (AMI) among patients with serious mental illness (SMI). Hypotheses were that invasive coronary interventions, including catheterization and revascularization, would be lower in cases compared to controls, and that the adverse outcomes of inpatient mortality, AMI recurrence, and subsequent hospitalization due to other cardiovascular diseases would be higher in cases compared to controls.

## 8.2 Method

### 8.2.1 Cases

The case samples were patients with schizophrenia or bipolar disorder from the case cohorts (described in **Chapter 6.2 ~ 6.3**) who had an AMI episode between 1996 and 2007. The first such AMI episode was defined as the 'index episode'.

### 8.2.2 Controls

The control samples were people from the comparison cohort (described in **Chapter 6.2 ~ 6.3**) who had an AMI episode between 1996 and 2007. The first such AMI episode was defined as the 'index episode'.

### 8.2.3 Main outcome variables

The main outcome variables on intervention after AMI are described in **Chapter 6.6~6.7**, and displayed in **Table 6.4.** If the discharge date of first AMI hospitalization matched the admission date of the next hospitalization, records of intervention receipts in these hospitalizations were merged and managed as care for the same AMI episode. We also investigated 30-day inpatient mortality as an outcome and

separately investigated rates of revascularization among those who have received catheterization.

Additional analyses included examining whether the following diagnoses co-occurred on the hospital discharge note after the index AMI episode as proxy measures of AMI severity (shown in **Table 8.1**): congestive heart failure, cardiogenic shock, conduction disorders, including second- or third-degree atrioventricular block, atrial fibrillation or flutter, cardiac dysrhythmias, and acute or chronic respiratory failure.

**Table 8.1 ICD-9-CM codes for complications during the index AMI episode**

| ICD-9-CM codes | Diagnosis for previous or co-occurring cardiovascular diseases |
|---|---|
| 428.XX | Congestive heart failure |
| 785.XX | Cardiogenic shock |
| 426.XX | Atrioventricular block |
| 427.XX | Cardiac dysrhythmias |
| 518.XX | Chronic respiratory failure |

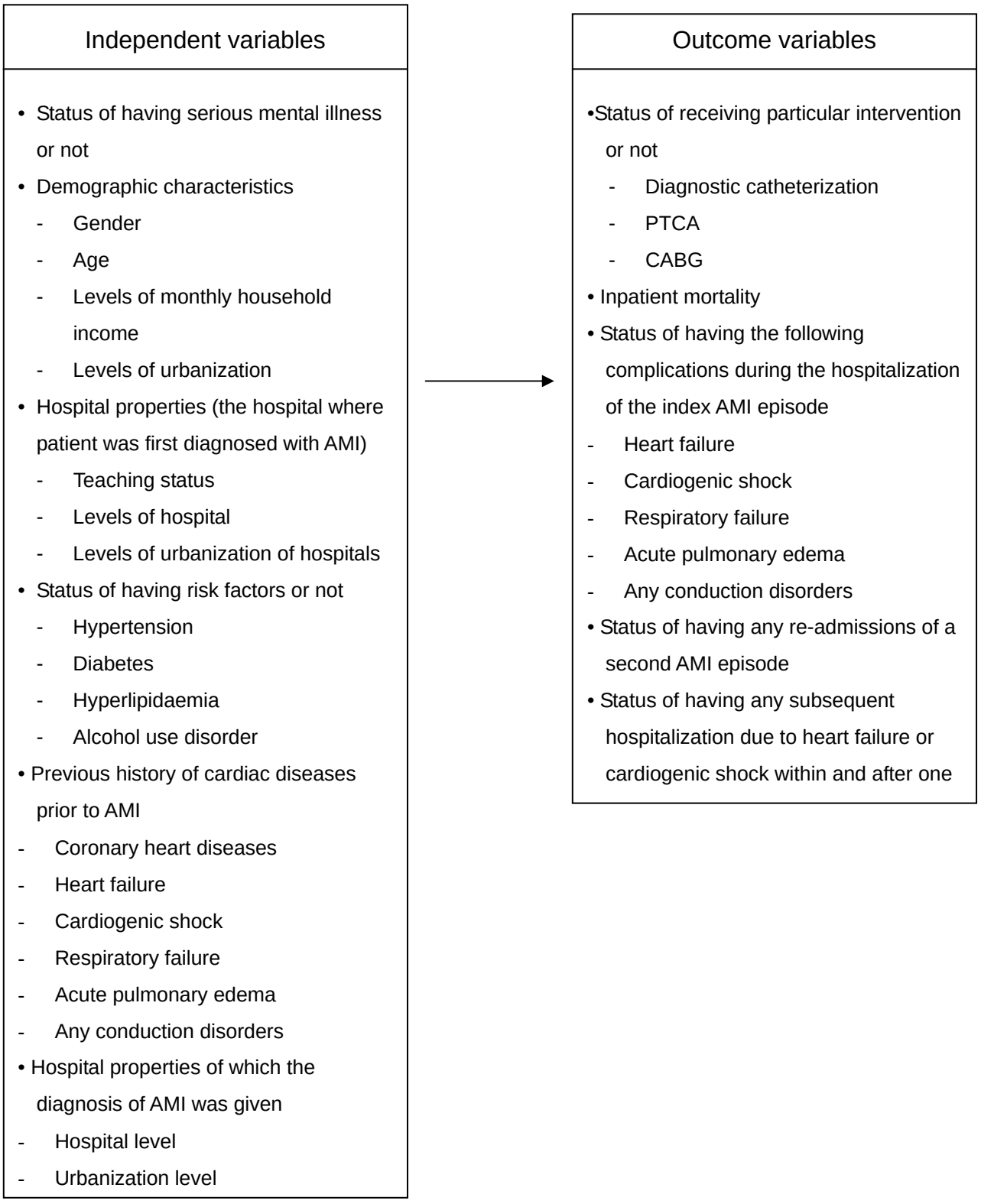
Finally, the following adverse outcomes were compared: 30-day inpatient mortality, proportions of re-admission with a second AMI episode, and subsequent hospitalization due to heart failure or cardiogenic shock within and after one year of the index AMI.

The following covariates (described in **Chapter 6.5**) were considered: demographic characteristics, cardiovascular risk factors (previous diagnoses of hypertension, diabetes, hyperlipidaemia, and alcohol use disorders prior to AMI). In addition the following factors were considered that might affect the receipt of diagnostic procedures or revascularization: previous history of cardiac diseases (coronary artery disease, heart failure, cardiogenic shock, respiratory failure, acute pulmonary edema, or any conduction disorder), and hospital properties (hospital level, geographical location, urbanization level, and teaching status, all obtained and classified using methods from previous research (Lin et al., 2006)). **Figure 8.1** summarises the analysis plan.

### 8.2.4 Statistical analysis

SAS version 9 for Windows (SAS Institute, Cary, NC) was used for data management and analysis. All covariates, including demographic characteristics and cardiovascular risk factors were initially compared between the cohorts using $\chi 2$ and Student t tests. Next, intervention receipt and inpatient mortality after AMI were calculated and compared between cohorts. Logistic regression analyses were carried out to examine the independent effects of having schizophrenia or bipolar disorder on the outcomes of intervention receipts, inpatient mortality, co-occurring diagnoses of complications, re-admissions of AMI, or subsequent hospitalization due to heart failure or cardiogenic shock within and after one year of the index AMI. Odds ratios were calculated with 95% confidence intervals. The analysis was divided into four stages. In the first stage, procedures of any catheterization or revascularization were modeled as dependent variables with respect to their associations with psychiatric diagnosis, adjusting for demographic and clinical covariates. Second, among people who were offered catheterization, similarly adjusted logistic regression analyses were carried out to examine the subsequent revascularization as an outcome. Third, odds of 30-day mortality were compared between people with or without severe mental disorders and adjusted not only for the above covariates but also for receipt of any catheterization or revascularization as potential mediators. Fourth, odds of re-admissions due to second AMI, or hospitalizations due to heart failure or cardiogenic shock within and after one year among those who discharged alive from their index AMI episode were analyzed.

**Figure 8.1 Concept of analysis for evaluating the intervention receipts, inpatient mortality, and inpatient complication following an AMI in people with or without serious mental illness**



## 8.3 Results

### 8.3.1 Sample characteristics

After applying inclusion/exclusion criteria, a total of 3,361 adult patients with incident AMI between 1996 and 2007 were identified, of whom 591 (17.6%) and 243 (7.2%) had a diagnosis of schizophrenia and bipolar disorder respectively, with 2,527 controls. Of cases with schizophrenia and bipolar disorder, 24 (4.1%) and 45 (18.5%) respectively were present on the LHID2000 dataset alone, implying that they had not received mental health impatient care before 2000. **Table 8.2** summarises the characteristics of the cohorts. The mean (SD) age at recorded AMI was 57.1 (15.4) years for people with schizophrenia, 64.2 (15.4) years in people with bipolar disorder, and 66.8 (13.8) years in the comparison cohort. Significant differences were found between cohorts in the mean ages of first AMI episode between three groups (ANOVA F 110.5, df 2, $p<0.001$) and in almost all categorical variables apart from history of previous cardiac diseases) between people with and without serious mental illness (all p-values $<0.05$). Patients with schizophrenia had a lower income level and were more likely to be diagnosed with diabetes, hyperlipidaemia, and alcohol use disorders prior to index AMI compared with the controls. Regarding intervention receipt, 24.1% (n=811) of all sample members received catheterization during their index AMI episode. Among these, 73.3% (n=595) received PTCA and 8.4% (n=68) received CABG. Less than 2% (n=9) received both procedures. Both mental disorder groups were less likely to receive diagnostic procedures (i.e. catheterization) and revascularization (i.e. PTCA and CABG) of AMI, or to be diagnosed in medical centers or teaching hospitals (all $p<0.001$ from chi-square test, df 1).

**Table 8.2 Between-cohort comparison of demographic and health / healthcare characteristics**

| | No serious mental illness (n= 2,527) | Schizophrenia ( n= 591) | Bipolar disorder ( n= 243 ) | P value |
|---|---|---|---|---|
| Mean (SD) age at index AMI episode | 66.8 (13.8) | 57.1 (15.4) | 64.2 (15.4) | <0.001 |
| Age group (%) | | | | |
| 18~35 | 5.7 | 15.2 | 6.2 | <0.001 |
| 36~45 | 13.7 | 22.5 | 12.4 | |
| 46~55 | 17.6 | 21.2 | 14.4 | |
| 56~65 | 26.4 | 16.9 | 18.5 | |
| 66~75 | 26.7 | 15.6 | 27.2 | |
| 76 and above | 10.1 | 8.6 | 21.4 | |
| Gender (%) | | | | 0.02 |
| Men | 64.9 | 60.1 | 58.4 | |
| Women | 35.1 | 39.9 | 41.6 | |
| Levels of urbanization (%) | | | | 0.02 |
| 1 (least urbanized) (reference group) | 13.6 | 14.2 | 4.5 | |
| 2 | 15.6 | 17.1 | 21.8 | |
| 3 | 15.0 | 13.0 | 15.6 | |
| 4 | 29.6 | 32.0 | 29.2 | |

| | | | | |
|---|---|---|---|---|
| 5 (most urbanized) | 26.2 | 23.7 | 28.8 | |
| Average monthly income NT$ (SD) | 11138.0 (14781.1) | 6442.5 (11472.8) | 7074.7 (13195.8) | <0.001 |
| Monthly income (%) | | | | <0.001 |
| NT$ 0 (reference group) | 32.0 | 25.9 | 34.2 | |
| NT$ 1~15840 | 23.8 | 50.0 | 41.2 | |
| NT$ 15841 ~ 25000 | 35.7 | 20.1 | 18.1 | |
| ≧NT$ 25001 | 8.5 | 4.2 | 6.6 | |
| Hypertension (%) | 10.3 | 52.6 | 50.6 | <0.001 |
| Diabetes (%) | 22.4 | 38.4 | 31.7 | <0.001 |
| Hyperlipidemia (%) | 19.9 | 27.6 | 27.6 | <0.001 |
| Alcohol use disorders (%) | 0.7 | 16.8 | 9.5 | <0.001 |
| History of previous cardiac diseases (%) | 21.3 | 21.2 | 25.1 | 0.37 |
| Hospital level at AMI diagnosis (%) | | | | <0.001 |
| Medical centers | 30.7 | 20.5 | 31.7 | |
| Regional hospitals | 32.0 | 29.1 | 22.6 | |
| District hospitals | 25.5 | 43.7 | 35.8 | |
| Others (reference group) | 11.8 | 6.8 | 9.9 | |
| Teaching hospital at AMI diagnosis (%) | 62.6 | 49.6 | 54.3 | <0.001 |
| Urbanization of hospital at AMI diagnosis (%) | | | | <0.001 |
| 1 ( least urbanized ) (reference group) | 4.4 | 8.1 | 2.1 | |

| | | | | |
|---|---|---|---|---|
| 2 | 13.4 | 17.3 | 11.1 | |
| 3 | 11.5 | 12.9 | 11.1 | |
| 4 | 37.9 | 33.8 | 42.4 | |
| 5 ( most urbanized ) | 32.9 | 27.9 | 33.3 | |
| Cardiac complications after AMI (%) | 19.3 | 18.3 | 18.1 | 0.80 |
| Receipt of catheterization (%) | 27.9 | 12.2 | 14.0 | <0.001 |
| Receipt of any PTCA or CABG (%) | 23.9 | 9.0 | 12.8 | <0.001 |

[a]Calculated by t-test or ANOVA for continuous variables, and chi-square test for other categorical variables.

### 8.3.2 Catheterization and revascularization following AMI in people with serious mental illness

Adjusted associations between case status and receipt of catheterizations and revascularization are summarized in **Table 8.3(a)** and **8.3(b)** Reduced likelihood of receiving these procedures persisted in the two case groups after adjusting for different covariates. Among those who were offered catheterization, people with mental disorder were less likely to receive revascularization, although this fell short of statistical significance (**Table 8.4**).

**Table 8.3(a) Odds ratios of catheterizations and revascularizations following AMI in people with and without schizophrenia (n=3118)**

| | **Receipt of catheterization** Odds ratio | **Receipt of revascularization** Odds ratio |
|---|---|---|
| Unadjusted OR | **0.36 ( 0.28 ~ 0.47 )** | **0.31 ( 0.23 ~ 0.42 )** |
| Model 1: adjusted for demographic characteristics (age of index AMI, gender, levels of income and urbanizations) | **0.35 ( 0.27 ~ 0.46 )** | **0.30 ( 0.22 ~ 0.41 )** |
| Model 2: adjusted for demographic characteristics, cardiovascular risk factors, and previous cardiac history | **0.33 ( 0.24 ~ 0.46 )** | **0.31 ( 0.22 ~ 0.45 )** |
| Model 3: adjusted for demographic characteristics, cardiovascular risk factors, previous cardiac history, and hospital properties | **0.38 ( 0.27 ~ 0.53 )** | **0.35 ( 0.24 ~ 0.51 )** |
| Model 4: adjusted for demographic characteristics, cardiovascular risk factors, previous cardiac history, hospital properties, and inpatient complications | **0.37 ( 0.26 ~ 0.53 )** | **0.35 ( 0.24 ~ 0.51 )** |

**Table 8.3(b) Odds ratios of catheterizations and revascularizations following AMI in people with and without bipolar disorder (n=2770)**

| | **Receipt of catheterization** Odds ratio | **Receipt of revascularization** Odds ratio |
|---|---|---|
| Unadjusted OR | **0.42 ( 0.29 ~ 0.61 )** | **0.47 ( 0.32 ~ 0.69 )** |
| Model 1: adjusted for demographic characteristics (age of index AMI, gender, levels of income and urbanizations) | **0.42 ( 0.29 ~ 0.61 )** | **0.47 ( 0.32 ~ 0.70 )** |
| Model 2: adjusted for demographic characteristics, cardiovascular risk factors, and previous cardiac history | **0.36 ( 0.23 ~ 0.54 )** | **0.42 ( 0.27 ~ 0.65 )** |
| Model 3: adjusted for demographic characteristics, cardiovascular risk factors, previous cardiac history, and hospital properties | **0.38 ( 0.24 ~ 0.59 )** | **0.47 ( 0.30 ~ 0.74 )** |
| Model 4: adjusted for demographic characteristics, cardiovascular risk factors, previous cardiac history, hospital properties, and inpatient complications | **0.38 ( 0.24 ~ 0.59 )** | **0.47 ( 0.30 ~ 0.74 )** |

**Table 8.4 Odds ratios of revascularization after AMI among people who received catheterization**

| | **Receipt of revascularization** | |
|---|---|---|
| | Schizophrenia (n=72) vs. control (n=705) Odds ratio | Bipolar disorder (n=34) vs. control (n=705) Odds ratio |
| Unadjusted OR | 0.58 ( 0.34 ~ 1.01 ) | 0.73 ( 0.32 ~ 1.64 ) |
| Model 1: adjusted for demographic characteristics (age of index AMI, gender, levels of income and urbanizations) | **0.53 ( 0.30 ~ 0.93 )** | 0.72 ( 0.32 ~ 1.64 ) |
| Model 2: adjusted for demographic characteristics, cardiovascular risk factors, and previous cardiac history | 0.60 ( 0.30 ~ 1.20 ) | 0.68 ( 0.28 ~ 1.66 ) |
| Model 3: adjusted for demographic characteristics, cardiovascular risk factors, previous cardiac history, and hospital properties | 0.59 ( 0.29 ~ 1.17 ) | 0.67 ( 0.27 ~ 1.66 ) |
| Model 4: adjusted for demographic characteristics, cardiovascular risk factors, previous cardiac history, hospital properties, and inpatient complications | 0.59 ( 0.29 ~ 1.18 ) | 0.68 ( 0.28 ~ 1.68 ) |

### 8.3.3 30-day inpatient mortality in people with or without schizophrenia and bipolar disorder

**Table 8.5** summarizes 30-day inpatient mortality and onset of cardiovascular complications. Patients with schizophrenia were found to have significantly higher inpatient mortality (chi-square 19.4, df 1, $p < 0.001$) than controls, despite the fact that both mental disorder groups had similar frequencies of complications compared to the controls.

Odds ratios of inpatient mortality in people with or without mental disorder are analyzed further in **Table 8.6**. Adjustments resulted in strengthened associations with schizophrenia (principally following adjustment for demographic factors), and attenuated associations with bipolar disorder. Associations with cardiovascular complications remained non-significant after adjustment apart from that between schizophrenia and respiratory failure (**Table 8.7**).

**Table 8.5 Inpatient mortality and complications following AMI**

| | No serious mental illness | Schizophrenia | Schizophrenia vs control | | Bipolar disorder | Bipolar disorder vs control | |
|---|---|---|---|---|---|---|---|
| | n = 2527 | n = 591 | chi-square (DF) | p | n = 243 | chi-square (DF) | p |
| Inpatient mortality (%) | 5.54 | 10.49 | 19.37 (1) | **<0.001** | 7.00 | 0.88 (1) | 0.35 |
| New-onset of any cardiovascular complication during the index AMI episode (%) | 19.27 | 18.27 | 0.31 (1) | 0.58 | 18.11 | 0.19 (1) | 0.66 |
| Heart failure | 8.31 | 7.28 | 0.69 (1) | 0.41 | 7.82 | 0.07 (1) | 0.79 |
| Cardiogenic shock | 7.00 | 7.28 | 0.05 (1) | 0.82 | 5.76 | 0.53 (1) | 0.47 |
| Respiratory failure | 7.48 | 8.97 | 1.48 (1) | 0.22 | 6.58 | 0.26 (1) | 0.61 |
| Acute pulmonary edema | 3.32 | 2.54 | 0.96 (1) | 0.33 | 3.70 | 0.10 (1) | 0.75 |
| Any conduction disorder | 4.83 | 3.05 | 3.55 (1) | 0.06 | 4.12 | 0.25 (1) | 0.62 |

**Table 8.6 Odds ratios of inpatient mortality following AMI in people with and without serious mental illness**

| | Schizophrenia vs. control<br>Odds ratio | Bipolar disorder vs. control<br>Odds ratio |
|---|---|---|
| Unadjusted OR | **2.00 ( 1.46 ~ 2.73 )** | 1.28 ( 0.76 ~ 2.16 ) |
| Model 1: adjusted for demographic characteristics (age of index AMI, gender, levels of income and urbanizations) | **2.68 ( 1.92 ~ 3.74 )** | 1.34 ( 0.79 ~ 2.28 ) |
| Model 2: adjusted for demographic characteristics, cardiovascular risk factors, and previous cardiac history | **2.62 ( 1.77 ~ 3.90 )** | 1.20 ( 0.67 ~ 2.14 ) |
| Model 3: adjusted for demographic characteristics, cardiovascular risk factors, previous cardiac history, and hospital properties | **2.79 (1.87 ~ 4.17 )** | 1.21 ( 0.68 ~ 2.18 ) |
| Model 4: adjusted for demographic characteristics, cardiovascular risk factors, previous cardiac history, hospital properties, and inpatient complications | **2.97 ( 1.93 ~ 4.58 )** | 1.30 ( 0.70 ~ 2.43) |
| Model 5: adjusted for demographic characteristics, cardiovascular risk factors, previous cardiac history, hospital properties, inpatient complications, and any receipt of catheterization or revascularization | **2.68 ( 1.73 ~ 4.15 )** | 1.19 ( 0.63 ~ 2.22 ) |

**Table 8.7 Odds ratios of cardiovascular complication being diagnosed during the index AMI episode in people with and without serious mental illness**

| | Schizophrenia group vs. comparison group | | Bipolar group vs. comparison group | |
|---|---|---|---|---|
| | Unadjusted OR | Adjusted OR | Unadjusted OR | Adjusted OR |
| New onset of any cardiovascular complications during the index AMI episode | 0.94 ( 0.74 ~ 1.18 ) | 1.06 ( 0.82 ~ 1.37) | 0.93 ( 0.66 ~ 1.30 ) | 0.75 ( 0.53 ~ 1.07 ) |
| New onset of heart failure during the index AMI episode | 0.87 ( 0.62 ~ 1.22 ) | 0.99 ( 0.68 ~ 1.44 ) | 0.94 ( 0.57 ~ 1.53 ) | 0.78 ( 0.47 ~ 1.30 ) |
| New onset of cardiogenic shock during the index AMI episode | 1.04 ( 0.74 ~ 1.47 ) | 1.20 ( 0.83 ~ 1.75 ) | 0.81 ( 0.46 ~ 1.42 ) | 0.67 ( 0.38 ~ 1.18 ) |
| New onset of respiratory failure during the index AMI episode | 1.22 ( 0.89 ~ 1.68 ) | **1.52 ( 1.07 ~ 2.15 )** | 0.87 ( 0.51 ~ 1.48 ) | 0.70 ( 0.41 ~ 1.20 ) |
| New onset of acute pulmonary edema during the index AMI episode | 0.76 ( 0.43 ~ 1.32 ) | 0.82 ( 0.45 ~ 1.50 ) | 1.12 ( 0.56 ~ 2.25 ) | 1.19 ( 0.57 ~ 2.46 ) |

Adjusted for age of first AMI, gender, levels of income and urbanization, cardiovascular risk factors of hypertension, diabetes, hyperlipidaemia, and alcohol use disorder

### 8.3.4 Hospitalizations due to AMI, heart failure, or cardiogenic shock within and after one year of the index AMI episode

There were no significant elevations in the odds ratios of re-admissions due to second AMI episode or due to heart failure in patients with psychiatric diagnosis, however, the odds of re-admission due to cardiogenic shock were significantly higher in the psychiatric groups after adjustment. (**Table 8.8(a) ~8.8(b)**)

**Table 8.8(a) Re-admissions due to second episode of AMI, heart failure, cardiogenic shock, or other conduction problems**

| | No serious mental illness | Schizophrenia | Schizophrenia vs control | | Bipolar disorder | Bipolar disorder vs control | |
|---|---|---|---|---|---|---|---|
| | n = 2527 | n = 591 | chi-square (DF) | p | n = 243 | chi-square (DF) | p |
| Re-admission of second AMI after one month and before a year after the discharge of index AMI (%) | 2.18 | 2.37 | 0.082 (1) | 0.77 | 3.29 | 1.24 (1) | 0.27 |
| Re-admission of second AMI one year after the discharge of index AMI (%) | 3.09 | 2.03 | 1.91 (1) | 0.17 | 3.29 | 0.03 (1) | 0.86 |
| New onset of heart failure after the discharge of index AMI (%) | 15.79 | 12.86 | 3.18 (1) | 0.07 | 15.64 | 0.004 (1) | 0.95 |
| New onset of cardiogenic shock after the discharge of index AMI (%) | 5.74 | 7.28 | 2.00 (1) | 0.16 | 9.88 | 6.63 (1) | **0.01** |
| New onset of conduction problems[1] after the discharge of index AMI (%) | 4.04 | 3.72 | 0.12 (1) | 0.73 | 2.47 | 1.45 (1) | 0.23 |

**Table 8.8(b) Odds ratios of re-admissions due to AMI or other cardiovascular complications after the index AMI episode in people with and without serious mental illness**

| | Schizophrenia group vs. comparison group | | Bipolar group vs. comparison group | |
|---|---|---|---|---|
| | Unadjusted OR | Adjusted OR[2] | Unadjusted OR | Adjusted OR[2] |
| Re-admission of second AMI after one month and before a year after the discharge of index AMI | 1.09 ( 0.60 ~ 1.98 ) | 1.05 ( 0.52 ~ 2.12 ) | 1.53 ( 0.72 ~ 3.25 ) | 1.22 ( 0.53 ~ 2.81 ) |
| Re-admission of second AMI one year after the discharge of index AMI | 0.65 ( 0.35 ~ 1.20 ) | 0.78 ( 0.38 ~ 1.61 ) | 1.07 ( 0.51 ~ 2.24 ) | 1.64 ( 0.46 ~ 2.38) |
| New onset of heart failure after the discharge of index AMI | 0.79 ( 0.61 ~ 1.02 ) | 0.96 ( 0.70 ~ 1.32 ) | 0.99 ( 0.69 ~ 1.42 ) | 1.19 ( 0.80 ~ 1.79 ) |
| New onset of cardiogenic shock after the discharge of index AMI | 1.29 ( 0.91 ~ 1.84 ) | **2.29 ( 1.48 ~ 3.55 )** | **1.80 ( 1.14 ~ 2.83 )** | **2.19 ( 1.32 ~ 3.64 )** |
| New onset of conduction disoreder[1] after the discharge of index AMI | 0.92 ( 0.58 ~ 1.47 ) | 1.13 ( 0.64 ~ 2.01 ) | 0.60 ( 0.26 ~ 1.39 ) | 0.69 ( 0.29 ~ 1.66 ) |

[1]Including ventricular tachycardia, ventricular fibrillation, atrioventricular block, and cardiac arrest

[2] Adjusted for demographic characteristics, cardiovascular risk factors, previous cardiac history, and inpatient complications

## 8.4 Discussions

### 8.4.1 Summary of the findings

In this analysis of national population-based administrative records, people with schizophrenia and bipolar disorder were found to have a significantly decreased likelihood of catheterizations and revascularizations during an AMI hospital episode than people without those mental disorders. Inpatient mortality remained three times higher in patients with schizophrenia compared to controls after adjusting for intervention receipt amongst other covariates. However, no evidence was found for raised inpatient mortality in patients with bipolar disorder. Only the complication of respiratory failure was significantly higher in patients with schizophrenia. Although no differences in the recurrence of AMI compared to general population, subsequent hospitalizations due to cardiogenic shock after discharge of index AMI was higher in patients with schizophrenia and bipolar disorder.

### 8.4.2 Decreased likelihood of intervention receipt in schizophrenia and bipolar disorder

The finding that both the schizophrenia and bipolar disorder groups were less than half as likely to receive invasive coronary interventions than controls is supported by previous research reporting odds ratios ranging from 0.27 to 0.93 (Druss et al., 2000; Jones LE & Carney, 2005; Kisely et al., 2009; Lawrence DM et al., 2003; Mitchell & Lawrence, 2011; Young & Foster, 2000). Thus, this finding raised the possibility of severe inequalities in service receipt following AMI for patients with SMI, although accepting that the case samples had relatively high morbidity as they were enriched by people who had received inpatient mental health care. Levels of severity for the index AMI episode, as far as these could be estimated from the data available, were similar between people with or without mental disorder and therefore do not clearly account for the difference in procedure receipt.

Several reasons have been suggested to underlie reduced medical care receipt in people with mental disorders. These include socioeconomic disadvantage and physician bias (Petersen et al., 2003; Schulman et al., 1999), inaccurate decisions (Graber et al., 2000; Petersen et al., 2003), and patient and/or family preferences, levels of adherence, or quality of therapeutic alliances (DiMatteo et al., 2000; Petersen et al., 2003). Reduced access to appropriate health insurance has also been cited (Druss & Rosenheck, 1998). The healthcare context for the findings presented here should therefore be considered. Economic disparities in Taiwan are less likely to be an underlying factor because of a healthcare system which has near-universal coverage comparable to systems in the UK and Canada (Kisely et al., 2009) and which entails very low out-of-pocket expenses or no cost sharing for people with serious mental illness at the point of delivery. As has been found in other settings (Druss et al., 2000), rates of revascularization among patients who underwent catheterization did not differ significantly between those with and without mental disorders (although a disadvantage for the schizophrenia group came close to significance), suggesting that the reduced access lay more at the point of investigation rather than at the point of management. Previous research has considered a variety of factors potentially underlying physician decision-making in people with mental disorders including perceived non-compliance, smoking habits, or cooperation with post-operative care as a reason for reduced cardiovascular interventions (Penn & Martin, 1998; Schulman et al., 1999). Although the nature of the data analyzed did not allow in-depth evaluation of physician behaviour, it is noteworthy that substantial inequalities were still found in a healthcare system that remunerates physicians on the basis of procedure receipt with no maximum limit on the total services a physician can provide and be paid for each month when appropriate managements were given. Conscious or unconscious judgments by

physicians concerning procedures performed in people with severe mental disorder may still be one of the reasons for the observed inequality.

In Taiwan, since 95% of people with serious mental illness live with friends, families, or other relatives (Hou et al., 2008; Song, 1999), it is important to consider the role that families play in healthcare decision making (Chou et al., 1992; Hou et al., 2008; Wu CC, 1993). As a consequence, it is also important to investigate further whether any inequality in intervention access might have arisen because of adequacy of information provided to facilitate decision-making where capacity is lacking (Druss et al., 2000), and to clarify the extent to which family empowerment and education interventions could improve the situation are also in need.

### 8.4.3 Raised inpatient mortality during AMI admission in patients with schizophrenia but not bipolar disorder

The 2-fold increased likelihood of 30-day inpatient mortality in people with schizophrenia was substantially stronger than that reported by previous literature (where odds ratios have ranged from 1.19 to 1.56) (Abrams et al., 2009; Kisely et al., 2009; Kurdyak et al., 2012). Patients with bipolar disorder on the other hand showed no significant mortality elevation, although this group were relatively small in size and, as mentioned, the hierarchical classification system may have resulted in selected cases. Findings should therefore be interpreted with caution, and further research is still required to establish reasons for the discrepancy in mortality and the disadvantage of intervention receipt for the two mental disorders, potentially exploring different levels of cognitive function, judgment, affective symptoms, or behavioural, and social performances between the two groups. It is also possible that there were underlying differences in vulnerability or vascular risk factors, since it was only possible to adjust for known and recorded disorders. As mentioned earlier,

cardiovascular outcomes in bipolar disorder have received much less research than those in schizophrenia and the findings here suggest discrepancies in outcome which may benefit from further investigation. One possible explanation may lie in attitudes to illness and help-seeking. Previous studies have found that despite higher objective levels of comorbidity, patients with schizophrenia report fewer physical symptoms or disorders than controls (Dworkin, 1994; Jeste et al., 1996; Phelan et al., 2001). Higher pain tolerance (Vahia et al., 2008) or lower sensitivity to pain because of antipsychotic use (Jeste et al., 1996) in schizophrenia might also be responsible. It is possible that delayed diagnosis or treatment might have occurred because communication failures (Dworkin, 1994; Mitchell & Lawrence, 2011; Robson & Gray, 2007), and it is important that medical personnel are more aware of the underlying disadvantage and the need to pay more attention to potential disease signs perhaps particularly in the context of active psychotic symptoms or where medically indicated treatments are refused (Phelan et al., 2001).

### 8.4.4 Significant elevation in the odds ratios of re-admissions due to cardiogenic shock

The result that the adjusted odds ratio of re-admissions due to cardiogenic shock after the first AMI episode was significantly higher in patients with serious mental illness compared with general population reflects the need of early recognition and treatment of this poor prognostic factor among psychiatric patients, especially since cardiogenic shock is the most common cause of death in patients hospitalized with AMI, and is associated with a poor prognosis and 50 ~ 80% mortality rates (Hollenberg et al., 1999; Topalian et al., 2008). Although there were no significant differences in re-admissions due to second AMI episode, heart failure or other conduction problems between people with or without serious mental illness, it should be borne in mind the possibility that the second AMI episode or other

cardiovascular complications went unrecognized by clinical attention in patients with psychiatric disorders, or patients died outside the hospital, and thus these diagnoses have not been detected. However, since 9.3% of recurrent myocardial infarction or 19.7% of ischemia were found to precipitate cardiogenic shock (Hochman et al., 2000; Topalian et al., 2008), it is important to educate patients discharged from an AMI episode and their families to aware the development of significant chest pain or other symptoms of AMI and to seek medical evaluations or interventions as soon as possible.

### 8.4.5 Strengths and Limitations

As well as the relatively large, nation-wide samples with statistical power advantages, a particular strength of the analysis lies in the fact that the data contained detailed records of relevant cardiovascular diagnoses and intervention receipts. An important limitation is that covariates of interest were confined to those represented in the dataset and information was not available, for example, on investigation results, specific symptom profiles, or the presence or not of previous AMI before 1996. Also, as mentioned in **Chapter 7**, it should be borne in mind that the generalisability of this study is limited to patients with schizophrenia or bipolar disorder who had previously received psychiatric inpatient care, and so are likely to represent groups with relatively severe mental disorder. Third, since a hierarchical algorithm was adopted, favoring a diagnosis of schizophrenia over bipolar disorder, cases with bipolar disorder were relatively restricted. Finally, there might be an issue with multiple analyses carried out in this study. However, adjustments in all models were decided *a priori*, and outcomes of intervention receipts, inpatient mortality, and one-year re-admissions were all part of the clinically meaningful processes and related to each other. Thus, multiplicity in adjustments was still needed.

# CHAPTER 9

# ASSOCIATION OF ACUTE MYOCARDIAL INFARCTION AND ANTIPSYCHOTIC USE IN PEOPLE WITH SCHIZOPHRENIA AND BIPOLAR DISORDER: A CASE-CROSSOVER STUDY

## 9.1 Objective

Taking advantage of a sizeable sample of patients with serious mental illness (SMI) derived from the large comprehensive national health insurance database, a case-crossover design was applied to investigate the associations between acute myocardial infarction (AMI) and recent antipsychotic use among people with SMI. Hypotheses were that antipsychotic exposure, especially typical antipsychotic, would be more common in the 'case' period compared to the 'control' period, and that the average dose of antipsychotic would be higher in the 'case' period compared to the 'control' period. The reason for hypothesizing that there would be more typical antipsychotic exposure in the 'case' period than in the 'control' period was because the short-term pathway leading to AMI might be associated with typical antipsychotic agents via conduction deficits (Vieweg, 2002; Wang, 2002; Wang, 2007) rather than cardiometabolic effects. Finally, different from the definition of 'case cohort' or 'control cohort' in **Chapters 7~8**, the 'case period' and 'control period' terms used in this chapter stand for the time periods 'proximal' or 'distal', respectively, to the index AMI episode.

## 9.2 Method

### 9.2.1 Study cohort

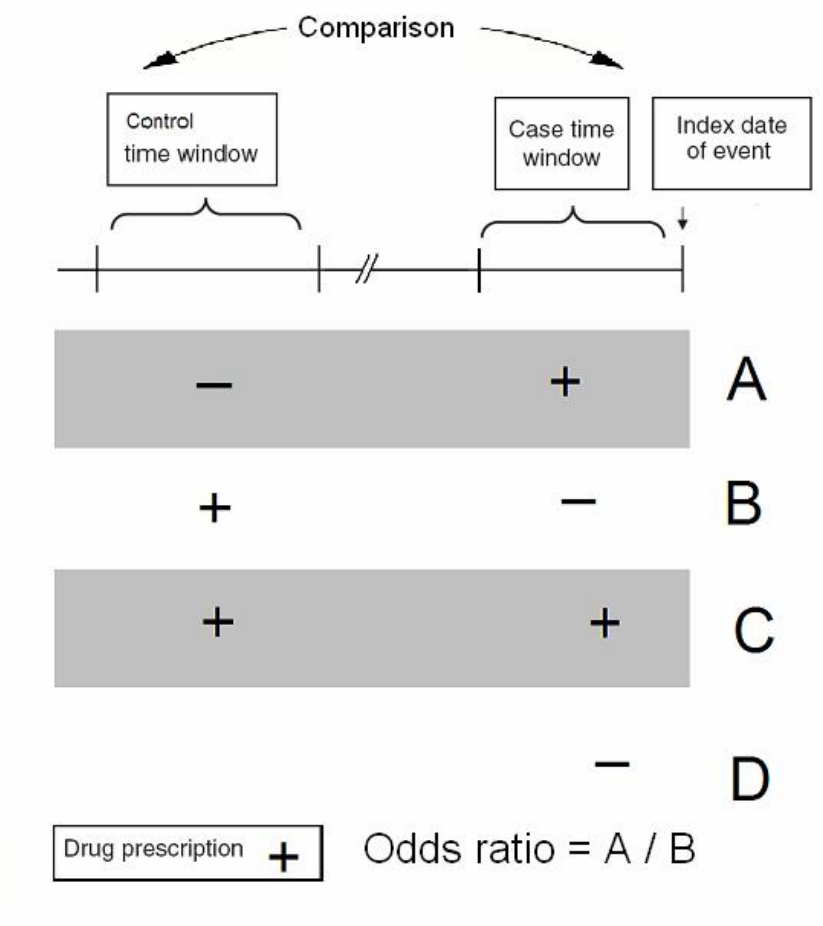
The study cohort were patients with schizophrenia or bipolar disorder from the PIMC and the LHIRD2000 (details described in **Chapter 6.2~ 6.3**) who had an episode of AMI in between 1996 to 2007.

### 9.2.2 Elements of the study design

As illustrated in **Figure 9.1**, a case-crossover design was applied in this study. This is a variant of the matched case-control design, but compares exposure status within individuals rather than between individuals: specifically between time periods

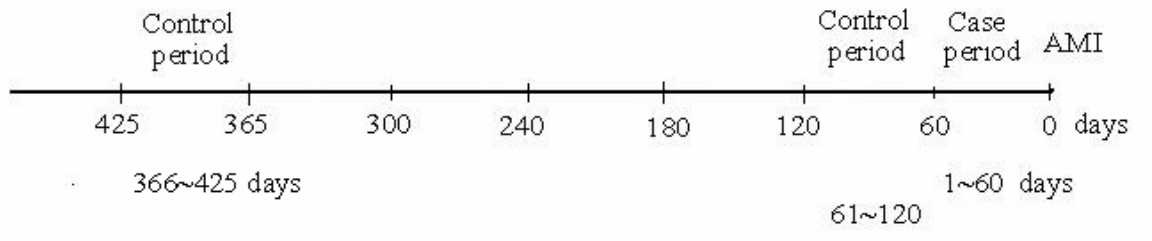
proximal and distal to the event of interest. The design provides a powerful means of removing the influence of between-individual differences as confounders (since individuals are their own controls) and is particularly suited to the investigation of short-term effects of exposures on the risk of acute outcomes (Maclure, 1991). In the study described here, a 60-day case and control time periods were chosen *a priori*, in order to be comparable to the study by Pariente et al. which quantified the incidence of AMI in pre-defined periods of 1~30 (acute), 31~60 (intermediate), 61~90 (prolonged) days after the first dispense of antipsychotic compared to the reference period (Pariente et al., 2012). Here in this study, the exposure status to antipsychotic was ascertained during the 60 day period prior to the index AMI episode and was compared with that during the preceding 60 days (i.e. 61-120 days prior to AMI) (see **Figure 9.2**). To check for consistency and to take account of any potential seasonal effect, an additional sensitivity analysis was carried out comparing the primary 60 day ‘case’ period to a 60 day ‘control’ period precisely one year previously.

**Figure 9.1 Application of the case-crossover design in the study**




The ratio of discordant pairs between the number of patients exposed in the case window (A) and that of the control window (B) was used as the estimation of the odds ratio.

**Figure 9.2 The 60-day case and control periods we used in this study**



### 9.2.3 Sample characteristics

Information was extracted from the database on demographic status (age and gender), and the presence or not of any diagnoses indicating increased cardiovascular risk (coronary artery diseases (ischemic heart diseases, angina pectoris, chronic ischemic heart disease or coronary atherosclerosis), cerebrovascular diseases, hypertension, diabetes, or hyperlipidaemia).

### 9.2.4 Antipsychotic exposure

From the 'Medical Expenditure and Prescription Claims subset' of the NHIRD, records were identified of antipsychotic prescription instances during the case or control time windows as the primary exposure (Anatomical Therapeutic Chemical (ATC) classification system: ATC code: N05A antipsychotic agents, as summarized in **Chapter 6.7** and **Table 6.5**). In order to quantify an individual's average daily dose, the Defined Daily Dose [DDD, or 'the assumed average maintenance dose per day for a drug used for its main indication in adults' (WHOCC, 2009), which had been previously applied in this database (Wu CS et al., 2011)], was calculated for each antipsychotic agent. This measure was applied in the following ways:

1. The summed total dose over the 12 months prior to AMI was calculated by adding up all the prescribed doses of antipsychotic agents within the 12- months period.
2. Average daily doses during case and control periods were calculated by using cumulative doses divided by cumulative exposure days.
3. The above two variables were further categorised into low and high ranges applying median values as the cut point for this.

Typical antipsychotics were defined as chlorpromazine, chlorprothixene, flupentixol, fluphenazine, haloperidol, levomepromazine, melperon, periciazine, perphenazine,

pimozide, pipamperone, prochlorperazine, promazine, thioridazine, and zuclopenthixol, and atypical antipsychotics were defined as amisulpride, clozapine, olanzapine, quetiapine, risperidone, sulpiride, ziprasidone, and aripiprazole (Enger et al., 2004; Farah, 2005; Meltzer, 2004).

### 9.2.5 Time-variant confounding factors

Confounding in a case-crossover study principally arises from other factors which may differ between case and control exposure periods (i.e. alternative explanations for any observed variation in the exposure). Hence, despite no more confounding effects of between-individual differences, other time-variant factors, such as prescriptions of antidepressants (tricyclics in particular), or cardiovascular medications (antithrombotic, antidiabetic, diuretic, antihypertensive, and lipid lowering agents) have been shown to have cardio-toxic (Glassman, 1998) or cardio-protective (Nakagawa et al., 2006) effects. Therefore, the following covariates were defined for the case and control time periods, and were adjusted in this respect (also see **Table 6.5** for ATC codes, (WHO, 2009)):

i) general healthcare contacts, quantified as the number of non-psychiatric outpatient visits;

ii) prescriptions of any antidepressant for at least one day.

iii) The presence of any cardiovascular medications (antithrombotic, antidiabetic, diuretic, antihypertensive, and lipid lowering agents) within each period was also calculated.

### 9.2.6 Statistical analysis

SAS version 9 for Windows (SAS Institute, Cary, NC) was used for data management and analysis. Matched pair analyses were carried out, pairing the case

and control time windows by each individual's unique identifier. Primary analyses compared any antipsychotic agent exposure as a binary variable between case and control time periods using conditional logistic regression models (PHREG procedure in SAS) to generate matched odds ratios from numbers of discordant pairs, followed by adjustment for potential confounders as described above. Sub-analyses on individuals with schizophrenia and bipolar disorder were then carried out separately, stratifying for the following factors: age at AMI (above and below median), gender, presence or not of a cardiovascular risk factor preceding the AMI, and the summed total antipsychotic dose (DDD above and below median value) for all antipsychotic prescriptions over the 12 months preceding the AMI. Interaction terms between antipsychotic exposure and these variables were tested. The frequencies of psychiatric hospitalization between case and control periods were also compared to contextualize findings. Further conditional logistic regression analyses were carried out to compare levels of average daily dose (DDD above and below median value), and use of typical vs. atypical antipsychotic agents between case and control periods. The test of whether there was a positive correlation between increased risk of AMI and higher average daily dose was examined by Wald chi-square test based on groups of low or high average daily dose (DDD) defined according to median value. Analyses were repeated using the second control period (12-15 months [366-425 days] before AMI) to check for consistency.

Finally, because matched odds ratios for exposure status (i.e. presence/absence of antipsychotic use) were derived only from discordant pairs (i.e. people with an exposure in one time period and without that exposure in the other), further analyses compared the average daily dose (DDD) of antipsychotic as a continuous variable between the two time periods in patients who had received antipsychotic agents at both times. Matched t-tests were used.

## 9.3 Results

After applying inclusion/exclusion criteria, a total of 834 cases with serious mental illness and incident AMI between 1996 and 2007 were identified: 591 (70.9%) with schizophrenia and 243 (29.1%) with bipolar disorder. **Table 9.1** summarizes sample characteristics. For all patients with antipsychotic exposure in the case period (n=384), the median average daily dose during this period was 0.50 DDD ($25^{th}$ and $75^{th}$ percentiles 0.25 and 0.92 respectively); for all patients with antipsychotic exposure in the control period (n=364), the median average daily dose during this period was 0.50 DDD ($25^{th}$ and $75^{th}$ percentiles 0.25 and 0.93 respectively).

**Table 9.1. Characteristics of the analyzed samples**

| | Schizophrenia ( n= 591) | Bipolar disorder ( n= 243 ) | Statistic, Degree of freedom (df), p value |
|---|---|---|---|
| Mean (SD) age at index AMI episode | 57.1 (15.4) | 64.2 (15.4) | F 36.6, df 1, p<0.001 |
| Gender (% female) | 39.9 | 41.6 | $\chi^2$ 0.19, df 1, p=0.66 |
| Levels of urbanization (%) | | | $\chi^2$ 19.3, df 4, p<0.001 |
| 1 (most urbanized) | 23.7 | 28.8 | |
| 2 | 32.0 | 29.2 | |
| 3 | 13.0 | 15.6 | |
| 4 | 17.1 | 21.8 | |
| 5 (least urbanized) | 14.2 | 4.5 | |
| Monthly income (%) | | | $\chi^2$ 9.16, df 3, p<0.05 |
| NT 0 | 25.9 | 34.2 | |
| NT$ 1~15840 | 50.0 | 41.2 | |
| NT$ 15841 ~ 25000 | 20.1 | 18.1 | |
| ≧NT$ 25001 | 4.2 | 6.6 | |
| Non-psychiatric medical visits the year before the AMI | | | F 17.8, df 1, p<0.001 |
| 0 times | 5.4 | 0.8 | |
| 1~22 times (below median) | 51.3 | 35.8 | |

| | | | |
|---|---|---|---|
| ≧ 23 times (above median) | 43.3 | 63.4 | |
| Any previous cardiovascular risk factors prior to AMI (%) | 78.7 | 82.7 | $\chi^2$ 1.74, df 1, p=0.19 |
| Hypertension | 54.3 | 60.5 | $\chi^2$ 2.67, df 1, p=0.10 |
| Diabetes | 38.6 | 33.3 | $\chi^2$ 2.03, df 1, p=0.18 |
| Hyperlipidemia | 28.1 | 30.0 | $\chi^2$ 0.32, df 1, p=0.63 |
| Alcohol use disorders | 13.4 | 8.6 | $\chi^2$ 3.64, df 1, p=0.07 |
| History of previous coronary heart diseases | 44.2 | 56.4 | $\chi^2$ 10.3, df 1, p<0.01 |
| History of previous cerebrovascular diseases | 6.4 | 6.2 | $\chi^2$ 0.02, df 1, p=0.89 |
| Total defined daily dose (DDD) of antipsychotic use in the 12 months prior to AMI | | | $\chi^2$ 60.1, df 1, p<0.001 |
| Total DDD <=67.7 (n = 255) | 41.0 | 82.7 | |
| Total DDD > 67.7 (n = 255) | 59.0 | 17.3 | |

### 9.3.1 Antipsychotic exposures in case and control periods

**Table 9.2** summarizes the results of case-crossover analyses on AMI and recent antipsychotic use in the 834 individuals with serious mental illness. For patients with antipsychotic exposure only in the case period (n=65), the median average daily dose during this period was 0.40 DDD ($25^{th}$ and $75^{th}$ percentiles 0.19 and 0.63 respectively); for patients with antipsychotic exposure only in the control period (n=45), the median average daily dose during this period was 0.25 DDD ($25^{th}$ and $75^{th}$ percentiles 0.17 and 0.81 respectively). Daily antipsychotic doses were therefore mostly below the recommended average maintenance dose in both periods. People who were male, diagnosed with schizophrenia, had no cardiovascular diagnoses, and were exposed to lower total dose of antipsychotic within the year prior to index AMI, were found to be significantly more likely to have antipsychotic exposure in the case period compared to the control period.

**Table 9.3** further summarizes the differences in average daily dose (above/below median DDD) and types of antipsychotic prescribed between case and control periods among patients with at least one antipsychotic prescription instance within the 12 months prior to AMI. Results showed no significant associations between average daily dose and AMI. However, there were more typical antipsychotic being prescribed in the case period compared to the control period. No significant differences were found in the frequency of psychiatric admissions between case and control periods (adjusted OR: 1.33, 95% CI: 0.84~2.08).

Regarding the stronger association between recent antipsychotic use and AMI in people with no previous cardiovascular disease diagnosis, average antipsychotic DDD during the case period was compared between people with and without

previous cardiovascular diagnoses but no significant differences were found (t 0.05, df 63, p=0.96).

Moreover, on further comparing the average daily dose between case and control periods in people with antipsychotic use in both (n=319), 32.9% of people had a higher average daily dose in the case period, 32.6% of people had a higher average daily dose in the control period, and 34.5% had the same average daily dose during both periods. A matched t-test found no significant difference in average daily dose between case and control periods in these concordant pairs (t = -1.04, df =318, p = 0.30).

**Table 9.2 Case-crossover analyses investigating the association between AMI and recent antipsychotic use, stratified by patient characteristics**

| | Any antipsychotic use in case (1-60 days) and control (61-120 days) periods prior to AMI (n) | | | | Association between recent antipsychotic use and AMI (OR, 95%CI)[a] | |
|---|---|---|---|---|---|---|
| | Use only in case period | Use only in control period | Use in both periods | Non-use in both periods | Unadjusted | Adjusted model [b] |
| Total sample | 65 | 45 | 319 | 405 | 1.44 (0.99 ~ 2.11) | 1.42 (0.97 ~ 2.08) |
| Psychiatric diagnosis | | | | | | |
| Schizophrenia (n= 591) | 49 | 29 | 270 | 243 | **1.69 (1.07 ~ 2.67)** | **1.66 (1.05 ~ 2.63)** |
| Bipolar disorder (n= 243) | 16 | 16 | 49 | 162 | 1.00 (0.50 ~ 2.00) | 0.98 (0.49 ~ 1.98) |
| Gender | | | | | | |
| Female ( n = 337 ) | 28 | 27 | 127 | 155 | 1.04 (0.61 ~ 1.76) | 1.04 (0.61 ~ 1.76) |
| Male ( n = 497 ) | 37 | 18 | 192 | 250 | **2.06 (1.17 ~ 3.61)** | **1.98 (1.12 ~ 3.48)** |
| Age (years) | | | | | | |
| 18~60 (n = 433) | 34 | 21 | 199 | 179 | 1.62 (0.94 ~ 2.79) | 1.60 (0.93 ~ 2.76) |
| >60 (n = 401) | 31 | 24 | 120 | 226 | 1.29 (0.76 ~ 2.20) | 1.25 (0.73 ~ 2.14) |
| Previous cardiovascular risk factors | | | | | | |
| No (n= 168) | 17 | 3 | 58 | 90 | **5.67 (1.66 ~ 19.33)** | **5.71 (1.67 ~ 19.53)** |
| Yes (n = 666) | 48 | 42 | 261 | 315 | 1.14 (0.76 ~ 1.73) | 1.11 (0.73 ~ 1.68) |

| | | | | | | |
|---|---|---|---|---|---|---|
| Summed antipsychotic dose (DDD) over the 12 months prior to AMI (n=510, excluding people who had not received any antipsychotic in the previous year) | | | | | | |
| <=67.7 (n = 255) | 52 | 30 | 104 | 69 | **1.73 (1.11 ~ 2.72)** | **1.71 (1.09 ~ 2.68)** |
| >67.7 (n = 255) | 13 | 15 | 215 | 12 | 0.87 (0.41 ~ 1.82) | 0.86 (0.41 ~ 1.81) |

[a]Calculated by McNemar's procedure for matched analyses (the ratio of subjects exposed only in the case period to subjects exposed only in the control period) and conditional logistic regression.

[b]Adjustment for non-psychiatric outpatient visits in the 60-day exposure periods

**Table 9.3. Risk of AMI and antipsychotic use within the 60-day risk period, by average defined daily dose and types of antipsychotic use among patients with at least one antipsychotic prescription instance within the 12 months prior to AMI (n=510)**

| | Any antipsychotic use in case (1-60 days) and control (61-120 days) periods prior to AMI (n) | | | | Association between recent antipsychotic use and AMI (OR, 95%CI)[a] | |
|---|---|---|---|---|---|---|
| | Use only in case period | Use only in control period | Use in both periods | Non-use in both periods | Unadjusted | Adjusted model 1[b] |
| Average daily dose (DDD) per day during exposed period (excluding people who had not received any antipsychotic in the previous year) | | | | | | |
| Above median | 36 | 27 | 144 | 303 | 1.33 (0.81 ~ 2.20) | 1.33 (0.81 ~ 2.19) |
| Type(s) of antipsychotic used during exposure period (excluding people who had not received any antipsychotic in the previous year) | | | | | | |
| Only typical | 59 | 39 | 249 | 163 | **1.51 (1.01 ~ 2.27)** | **1.50 (1.00 ~ 2.25)** |
| Only atypical | 13 | 10 | 122 | 365 | 1.40 (0.44 ~ 4.41) | 1.42 (0.45 ~ 4.48) |
| Combined | 7 | 5 | 51 | 447 | 1.40 (0.44 ~ 4.41) | 1.45 (0.46 ~ 4.61) |

[a] Calculated by McNemar's procedure for matched analyses (the ratio of subjects exposed only in the case period to subjects exposed only in the control period) and conditional logistic regression.

[b] Adjustment for non-psychiatric outpatient visits in the 60-day exposure periods

### 9.3.2 Sub-analyses in patients with schizophrenia

Antipsychotic use prior to AMI was then analyzed separately in people with schizophrenia and bipolar disorder. As summarized in **Table 9.4**, in people with schizophrenia more recent antipsychotic prescription was associated with AMI after adjusting for potential confounders, suggesting a 60% increased risk.

Having tested for statistical interactions, the association between AMI and more recent antipsychotic prescription was stronger in men (interaction term coefficient 3.43, 95% CI 1.29~9.14, p=0.014), in those without prior cardiovascular diagnoses (0.20, 0.04~0.93, p=0.041), and in patients with lower overall antipsychotic exposure over the previous year (0.61, 0.21~1.76, p=0.36), but there was no significant modification by age group (0.96, 0.34~12.28, p=0.78).

**Table 9.4. Case-crossover analyses investigating the association between AMI and recent antipsychotic use in patients with schizophrenia (n=591)**

| | Any antipsychotic use in case (1-60 days) and control (61-120 days) periods prior to AMI (n) | | | | Association between recent antipsychotic use and AMI (OR, 95%CI)[a] | |
|---|---|---|---|---|---|---|
| | Use only in case period | Use only in control period | Use in both periods | Non-use in both periods | Unadjusted | Adjusted model[b] |
| Total sample (n=591) | 49 | 29 | 270 | 243 | **1.69 (1.07 ~ 2.67)** | **1.60 (1.01 ~ 2.55)** |
| Gender | | | | | | |
| Women ( n = 236 ) | 19 | 20 | 106 | 91 | 0.95 (0.51 ~ 1.78) | 0.93 (0.49 ~ 1.77) |
| Men ( n = 355 ) | 30 | 9 | 164 | 152 | **3.33 (1.58 ~ 7.02)** | **3.10 (1.46 ~ 6.58)** |
| Age (years) | | | | | | |
| 18~60 (n = 346) | 30 | 16 | 182 | 118 | **1.88 (1.02 ~ 3.44)** | 1.81 (0.98 ~ 3.35) |
| >60 (n = 245) | 19 | 13 | 88 | 125 | 1.46 (0.72 ~ 2.96) | 1.37 (0.68 ~ 2.80) |
| Previous cardiovascular risk factors | | | | | | |
| No (n= 126) | 12 | 2 | 50 | 62 | **6.00 (1.34 ~ 26.79)** | **7.00 (1.49 ~ 32.91)** |
| Yes (n = 465) | 37 | 27 | 220 | 181 | 1.37 (0.83 ~ 2.25) | 1.26 (0.76 ~ 2.09) |
| Summed antipsychotic doses (DDD) over the 12 months prior to AMI (n=400, excluding people who had not received any antipsychotic in the previous year) | | | | | | |
| Below median (n = 200) | 38 | 20 | 97 | 45 | **1.90 (1.11 ~ 3.27)** | **1.90 (1.10 ~ 3.31)** |
| Above median (n = 200) | 11 | 9 | 173 | 7 | 1.22 (0.51 ~ 2.95) | 1.14 (0.46 ~ 2.80) |

[a]Calculated by McNemar's procedure for matched analyses (the ratio of subjects exposed only in the case period to subjects exposed only in the control period) and conditional logistic regression.

[b]Adjustment for non-psychiatric outpatient visits and antidepressant use in the 60-day exposure periods

Further analyses for patients with schizophrenia who had at least one antipsychotic prescription (**Table 9.5**) found no significant association between risk of AMI and recent exposure to higher antipsychotic average daily dose (i.e. above the 0.61 median DDD) after adjustment, nor was there a dose-response relationship (Wald chi-square = 1.08, df=1, p trend = 0.30). It seemed that the odds ratios for typical agents were significantly higher than those for atypical agents, although patients with discordant time periods for atypical antipsychotic agents were too small for further interpretation. The odds of any psychiatric admission were not found to differ between the case and control periods (OR=1.32, 95% CI 0.78 ~ 2.22).

Comparing the average daily dose between case and control periods in concordant pairs (i.e those who received antipsychotic prescription in both periods) of schizophrenia, a matched t-test revealed no significant difference (t = -0.43, df =269, p = 0.66).

A series of exploratory analyses were carried out to investigate further the primary finding in the group with schizophrenia. Additional adjustment for changes in cardiovascular medication use did not substantially alter the primary association (further adjusted odds ratio 1.56, 95% CI 0.98~2.48). Analyses using the alternative control period (1 year previously) are summarized in **Table 9.6** and indicate a stronger association between AMI and recent antipsychotic exposure.

**Table 9.5 Risk of AMI and antipsychotic use within the 60-day risk period, by average defined daily dose and types of antipsychotic use among schizophrenia with at least one antipsychotic prescription instance within the 12 months prior to AMI (n=400)**

| | Any antipsychotic use in case (1-60 days) and control (61-120 days) periods prior to AMI (n) | | | | Association between recent antipsychotic use and AMI (OR, 95%CI)[a] | |
|---|---|---|---|---|---|---|
| | Use only in case period | Use only in control period | Use in both periods | Non-use in both periods | Unadjusted | Adjusted model 1[b] |
| Average daily dose during exposed period | | | | | | |
| Above median | 28 | 26 | 124 | 222 | 1.08 (0.63 ~ 1.84) | 1.07 (0.63 ~ 1.83) |
| Type(s) of antipsychotic used during exposure period | | | | | | |
| Only typical | 45 | 26 | 213 | 116 | **1.73 (1.07 ~ 2.81)** | **1.71 (1.06 ~ 2.78)** |
| Only atypical | 10 | 6 | 102 | 282 | 1.67 (0.61 ~ 4.59) | 1.63 (0.59 ~ 4.49) |
| Combined | 6 | 4 | 44 | 346 | 1.50 (0.42 ~ 5.32) | 1.47 (0.41 ~ 5.23) |

[a]Calculated by McNemar's procedure for matched analyses (the ratio of subjects exposed only in the case period to subjects exposed only in the control period) and conditional logistic regression.

[b]Adjustment for number of non-psychiatric outpatient visits and antidepressants use in the 60-day exposure periods.

**Table 9.6. Sensitivity analyses comparing the case period to the control period one year prior to the AMI in people with schizophrenia**

| | Any antipsychotic use in case (1-60 days) and control (366-425 days) periods prior to AMI (n) | | | | Association between recent antipsychotic use and AMI (OR, 95%CI)[a] | |
|---|---|---|---|---|---|---|
| | Use only in case period | Use only in control period | Use in both periods | Non-use in both periods | Unadjusted | Adjusted model[b] |
| Total sample (n=591) | 95 | 45 | 224 | 227 | **2.11 (1.48 ~ 3.01)** | **4.20 (2.29 ~ 7.68)** |
| Gender | | | | | | |
| Women ( n = 236 ) | 38 | 21 | 87 | 90 | **1.81 (1.06 ~ 3.08)** | **4.46 (1.60 ~ 12.43)** |
| Men ( n = 355 ) | 57 | 24 | 138 | 138 | **2.38 (1.47 ~ 3.83)** | **4.19 (1.96 ~ 8.95)** |
| Age (years) | | | | | | |
| 18~60 (n = 346) | 54 | 25 | 158 | 109 | **2.16 (1.34 ~ 3.47)** | **3.56 (1.75 ~ 7.23)** |
| >60 (n = 245) | 41 | 20 | 66 | 118 | **2.05 (1.20 ~ 3.50)** | **6.81 (2.07 ~ 22.33)** |
| Previous cardiovascular risk factors | | | | | | |
| No (n= 126) | 21 | 4 | 41 | 60 | **5.25 (1.80 ~ 15.29)** | **6.30 (1.71 ~ 23.24)** |
| Yes (n = 465) | 74 | 41 | 183 | 167 | **1.81 (1.23 ~ 2.64)** | **3.89 (1.91 ~ 7.91)** |

[a]Calculated by McNemar's procedure for matched analyses (the ratio of subjects exposed only in the case period to subjects exposed only in the control period) and conditional logistic regression.

[b]Adjustment for non-psychiatric outpatient visits and antidepressant use in the 60-day exposure periods

### 9.3.3 Sub-analyses in patients with bipolar disorder

As shown in **Table 9.7**, there was no association between AMI and recent antipsychotic use in patients with bipolar disorder either before or after adjustment. However, it should be borne in mind that the case numbers for stratified analyses in bipolar group might be too small to be interpretable. No significant modifications by gender (interaction term coefficient 0.58, 95%CI 0.14~2.37, p=0.45), age group (0.95, 95%CI 0.54~1.70, p=0.87), prior cardiovascular risk factors (0.18, 95%CI 0.02~1.74, p=0.14), or summed dose of antipsychotic prescription within the year prior to AMI (2.45, 95%CI 0.54~11.24, p=0.25) were found.

**Table 9.7. Case-crossover analyses investigating the association between AMI and recent antipsychotic use in patients with bipolar (n=243)**

| | Any antipsychotic use in case (1-60 days) and control (61-120 days) periods prior to AMI (n) | | | | Association between recent antipsychotic use and AMI (OR, 95%CI)[a] | |
|---|---|---|---|---|---|---|
| | Use only in case period | Use only in control period | Use in both periods | Non-use in both periods | Unadjusted | Adjusted model[b] |
| Total sample (n=243) | 16 | 16 | 49 | 162 | 1.00 (0.50 ~ 2.00) | 0.98 (0.49 ~ 1.98) |
| Gender | | | | | | |
| Women ( n =101 ) | 9 | 7 | 21 | 64 | 1.29 (0.48 ~ 3.45) | 1.29 (0.48 ~ 3.49) |
| Men ( n = 142 ) | 7 | 9 | 28 | 98 | 0.78 (0.29 ~ 2.09) | 0.74 (0.27 ~ 2.02) |
| Age (years) | | | | | | |
| 18~60 (n = 87) | 4 | 5 | 17 | 61 | 0.80 (0.22 ~ 2.98) | 0.80 (0.21 ~ 3.01) |
| >60 (n = 156) | 12 | 11 | 32 | 101 | 1.09 (0.48 ~ 2.47) | 1.06 (0.47 ~ 2.43) |
| Previous cardiovascular risk factors | | | | | | |
| No (n= 42) | 5 | 1 | 8 | 28 | 5.00 (0.58 ~ 42.8) | 4.47 (0.51 ~ 39.2) |
| Yes (n = 201) | 11 | 15 | 41 | 134 | 0.73 (0.34 ~ 1.60) | 0.75 (0.34 ~ 1.64) |
| Summed antipsychotic dose (DDD) over the 12 months prior to AMI (n=110, excluding people who had not received any antipsychotic in the previous year) | | | | | | |
| Below median (n = 55) | 9 | 12 | 10 | 24 | 0.75 (0.32 ~ 1.78) | 0.73 (0.30 ~ 1.74) |
| Above median (n = 55) | 7 | 4 | 39 | 5 | 1.75 (0.51 ~ 5.98) | 1.76 (0.51 ~ 6.04) |

[a]Calculated by McNemar's procedure for matched analyses (the ratio of subjects exposed only in the case period to subjects exposed only in the control period) and conditional logistic regression.

[b]Adjustment for non-psychiatric outpatient visits and antidepressant use in the 60-day exposure periods

In patients with bipolar who received at least one prescription of antipsychotic within the year prior to AMI, further analyses (**Table 9.8**) found no significant differences between risk of AMI and exposures to lower or higher antipsychotic summed dose (above the 0.24 median DDD) or typical vs. atypical antipsychotic after adjustment. No significant trend of dose-response relationship (Wald chi-square = 1.25, df=1, p trend = 0.27) was observed. Among concordant pairs of people with bipolar disorder (n=49), no significant difference were found in average daily dose between case and control periods (t = -0.97, df =48, p = 0.34).

Similar to people with schizophrenia, results of additional analyses using a more distant control period one year previously revealed stronger associations between AMI and recent antipsychotic exposure (summarized in Table **9.9).**

**Table 9.8 Risk of AMI and antipsychotic use within the 60-day risk period, by average defined daily dose and types of antipsychotic use among bipolar with at least one antipsychotic prescription instance within the 12 months prior to AMI (n=110)**

| | Any antipsychotic use in case (1-60 days) and control (61-120 days) periods prior to AMI (n) | | | | Association between recent antipsychotic use and AMI (OR, 95%CI)[a] | |
|---|---|---|---|---|---|---|
| | Use only in case period | Use only in control period | Use in both periods | Non-use in both periods | Unadjusted | Adjusted model 1[b] |
| Average daily dose during exposed period | | | | | | |
| Above median | 11 | 8 | 22 | 69 | 1.38 (0.55 ~ 3.42) | 1.38 (0.55 ~ 3.42) |
| Type(s) of antipsychotic used during exposure period | | | | | | |
| Only typical | 14 | 13 | 36 | 47 | 1.08 (0.51 ~ 2.29) | 1.08 (0.51 ~ 2.29) |
| Only atypical | 3 | 4 | 20 | 83 | 0.75 (0.17 ~ 3.35) | 0.75 (0.17 ~ 3.36) |
| Combined | 1 | 1 | 7 | 101 | 1.00 (0.06 ~ 15.99) | 1.00 (0.06 ~ 17.62) |

[a] Calculated by McNemar's procedure for matched analyses (the ratio of subjects exposed only in the case period to subjects exposed only in the control period) and conditional logistic regression.

[b] Adjustment for number of non-psychiatric outpatient visits and antidepressants use in the 60-day exposure periods.

**Table 9.9. Sensitivity analyses comparing the case period to the control period one year prior to the AMI in people with bipolar disorder**

| | Any antipsychotic use in case (1-60 days) and control (366-425 days) periods prior to AMI (n) | | | | Association between recent antipsychotic use and AMI (OR, 95%CI)[a] | |
|---|---|---|---|---|---|---|
| | Use only in case period | Use only in control period | Use in both periods | Non-use in both periods | Unadjusted | Adjusted model[b] |
| Total sample (n=243) | 36 | 18 | 29 | 160 | **2.00 (1.14 ~ 3.52)** | **6.22 (2.07 ~ 18.71)** |
| Gender | | | | | | |
| Women ( n =101 ) | 16 | 9 | 14 | 62 | 1.78 (0.79 ~ 4.02) | **23.91 (2.40 ~ 238.1)** |
| Men ( n = 142 ) | 57 | 24 | 138 | 138 | **2.22 (1.01 ~ 4.88)** | 3.43 (0.93 ~ 12.59) |
| Age (years) | | | | | | |
| 18~60 (n = 87) | 12 | 4 | 9 | 62 | 3.00 (0.97 ~ 9.30) | **6.56 (1.28 ~ 33.55)** |
| >60 (n = 156) | 24 | 14 | 20 | 98 | 1.71 (0.89 ~ 3.31) | **6.46 (1.39 ~ 30.05)** |
| Previous cardiovascular risk factors | | | | | | |
| No (n= 42) | 9 | 2 | 4 | 27 | 4.50 (0.97 ~ 20.83) | **14.38 (1.84 ~ 112.4)** |
| Yes (n = 201) | 27 | 16 | 25 | 133 | 1.69 (0.913 ~ 3.13) | 3.53 (0.90 ~ 13.83) |

[a]Calculated by McNemar's procedure for matched analyses (the ratio of subjects exposed only in the case period to subjects exposed only in the control period) and conditional logistic regression.

[b]Adjustment for non-psychiatric outpatient visits and antidepressant use in the 60-day exposure periods

### 9.3.4 Differences between patients with schizophrenia and bipolar disorder

Considering differences between schizophrenia and bipolar disorder, atypical antipsychotic use within the 12 months prior to AMI was found to be more frequent in patients with schizophrenia than in those with bipolar disorder (11.5% and 6.4% respectively; chi-square = 4.73, DF=1, p=0.030), and the quantity of antipsychotic use over the 12 months prior to AMI was higher (mean (SD) summed DDDs 54.1 (90.3) and 13.8 (20.1) respectively; t =2.42, DF=8, p=0.042). The mean (SD) daily doses (DDD) of antipsychotic during the case period were 0.62 (0.52) in patients with schizophrenia and 0.25 (0.15) in those with bipolar disorder (t =2.77, DF=63, p=0.007). However, there were no marked differences in psychiatric hospitalization (9.0% and 7.0% respectively; chi-square = 0.88, DF=1, p=0.351) or combination of psychiatric hospitalization and antipsychotic prescription (5.9 % and 5.6 % respectively; chi-square = 0.10, DF=1, p=0.747) in the case period between the two disorders.

## 9.4 Discussions

### 9.4.1 Summary of main findings

There has long been speculation about antipsychotic agents as one of the potential reasons for higher risk of cardiovascular disease in people with SMI (Brauer et al., 2011). In this study, after adjusting for other potentially time-varying confounders, there was a 60% increased odds of recent antipsychotic exposure before AMI in people with schizophrenia in primary analyses, but the same was not observed in those with bipolar disorder. Within the group with schizophrenia, the association was significantly stronger in men, in people without previous cardiovascular diagnoses and in those with lower overall antipsychotic exposure during the 12 months preceding the AMI. However, AMI was not associated with the average dose of recent antipsychotic, so far as this could be ascertained, and it was not associated with an increase in the dose in people who were receiving antipsychotics during both comparison periods.

The key finding was that antipsychotic exposure was significantly more common in the 'case' period compared to the 'control' period in patients with schizophrenia. The importance of the timing was further supported in the additional analyses when the control period was separated from the case period. Although the statistical significance of the association was reduced after further adjustment for changes in cardiovascular medication, the odds ratio did not change substantially and the inclusion of this covariate might represent over-adjustment since initiation of cardiovascular medication might have been an early sign of the incipient outcome. In agreement with the hypothesis stated in **Chapter 5** that exposures of typical antipsychotic would be more common in the 'case' period than in the 'control period', it was revealed in **Table 9.5** that typical antipsychotic agents have been used more commonly only in the case period than in the control period in people with

schizophrenia. Regarding possible mechanisms, the known longer-term cardiovascular risks associated with atypical antipsychotic use mediated through insulin resistance and obesity (Newcomer, 2007) would not be captured in this particular research design which focused on investigating shorter-term relationships. These might be associated with other vascular processes (Pariente et al., 2012) or conduction deficits, as have been proposed as potential causes of sudden cardiac death (Straus et al., 2004; Suvisaari et al., 2009) and have been reported in association with typical antipsychotic agents (Suvisaari, 2009; Vieweg, 2002; Wang, 2007). It is important to bear in mind that, despite the positive association observed between recent antipsychotic exposure and AMI, since underlying mechanisms are still unclear, and the association might be accounted for by protopathic bias (i.e. the psychotic/physical state that led to the antipsychotic prescription), the interpretation of the key finding needs caution. Causal pathways and possible impacts clearly require further elucidation, particularly as the benefits of antipsychotic medication are likely to outweigh any increased risk of AMI, as described in previous literature demonstrating that lower mortality is associated with antipsychotic use in people with SMI (Tiihonen, 2009; Tiihonen, 2012).

As well as the primary association itself, the finding that the risk of AMI is higher in people with lower overall antipsychotic exposure over the 12 months prior to AMI suggests that new initiation of antipsychotic may be associated particularly with increased risk. Unfortunately the data available (based on prescription) did not allow investigation of specific administration patterns, for example, peak single doses and emergency administrations. There was also no measure of adherence to prescribed medication. Although overall dose during the 60 day exposure periods did not differ or modify the association of interest, it is possible that patterns of administration might have varied which would need investigating in a database with information on

administration rather than prescription. Another question which is difficult to address conclusively is the extent to which the risk factor for AMI being observed is the antipsychotic agent itself or the symptoms being treated. Against the latter possibility, there was no difference found in inpatient care between the case and control periods; however, no data were available on specific symptom severity. It should be noted that the highest risk groups were found to be men with schizophrenia who had been relatively antipsychotic-naïve over the preceding 12 months. The author feels that, taken together, these facts are more consistent with an effect of treatment rather than underlying disorder on AMI; however, further investigation is clearly required.

Contrary to expectations, the association between antipsychotic and AMI was found to be weaker rather than stronger in people with previous diagnoses of cardiovascular disease or cardiovascular risk factors compared to those without. An important consideration is that these data reflected recorded diagnoses and no data were available on measurements such as actual blood pressure or cholesterol levels. In particular, the group who had not received any cardiovascular diagnosis might have contained people with unrecognized morbidity who might be a group at particular risk, again an important issue requiring further investigation. If the antipsychotic agent itself can be considered a risk factor for AMI, one possible explanation for the observation is that administration may have been more cautious in people with known risk factors for cardiovascular disease. No evidence was found for differences in averaged antipsychotic doses; however, as previously mentioned, these may not reflect the pattern of administration such as the maximum single dose given.

In contrast to schizophrenia, associations between AMI and recent antipsychotic use appeared absent in bipolar disorder. Potential reasons for the discrepancy between the two mental disorders might be the difference in disease presentation and

prescription patterns of psychotropics: for example, the inclusion of other pharmacotherapy such as lithium or anticonvulsants for acute care, either instead of antipsychotic agents or as a partial replacement so that lower single doses were required. However, it is important to note that an association remained between bipolar disorder and more recent antipsychotic exposure when the case period was compared to a control period one year previously. An association is therefore still possible which for some reason was not present with a more contiguous control period, perhaps because of other causal pathways. It should also be borne in mind that because of the hierarchical algorithm applied, the sample with bipolar disorder were smaller in size and might be skewed to include less prominently psychotic syndromes. Thus, the result of negative findings in bipolar patients described here may not apply to all bipolar patients. However, further analysis broadening the sample by including 250 more people who had been diagnosed with both bipolar disorder and schizophrenia showed results similar to the primary finding for bipolar disorder (adjusted OR = 1.14, 0.70~1.87).

### 9.4.2 Strengths and Limitations

From knowledge to date, this is the first study to date using a case-crossover design to investigate the association between recent antipsychotic exposure and risk of acute myocardial infarction. The specific focus on patients with serious mental illness and the national sample are also novel features. Strengths of this study include the relatively large samples of people with clinically diagnosed mental disorders who experienced a hospitalized AMI, drawn from a data resource with near-universal national coverage. Data availability included prescriptions of antipsychotic and other medications. The case-crossover design has substantial advantages, compared to a traditional cohort study, of removing the influence of between-individual confounding although (as will be discussed) time-varying confounders within

individuals do require consideration. Sensitivity analyses altering the control period additionally supported the robustness of the primary finding.

Limitations include the fact that the majority of cases were drawn from a sub-register identifying people who had previously received inpatient mental health care and therefore the analysed sample represent cases with relatively severe illness which should be borne in mind when considering generalisability. In addition, the outcome was hospitalized AMI and would not include episodes which did not result in inpatient care or sudden deaths outside the hospital. Furthermore, as discussed earlier, there was limited depth of information about symptomatology. However, measurement errors in case or outcome ascertainments will have obscured rather than exaggerated the associations of interest. Finally, the study was limited in its ability to differentiate between individual antipsychotic agents (for example, on the basis of their receptor-binding profiles) because of insufficient statistical power.

# CHAPTER 10

# GENERAL CONCLUSIONS AND IMPLICATIONS

## 10.1 Summary of key findings

This thesis comprised investigations of three objectives: comparing risk of acute myocardial infarction (AMI) in people with/without serious mental illness (SMI), comparing intervention receipts following an AMI episode between these groups, and investigating short-term associations between AMI and recent antipsychotic exposure within the serious mental illness group. Key findings relevant to study objectives and hypotheses are listed below.

**Objective 1: 'To investigate the relative risk of acute myocardial infarction among patients with serious mental illness'**

(1) Hypothesis: Compared with the national population, people with SMI will have a higher risk of acute myocardial infarction, independent of age, sex, previous history of cardiovascular risk factors, and levels of monthly income and urbanization levels.

*Summary of key findings*:

This hypothesis was only partly supported. Comparing 25,652 individuals with SMI and 182,814 individuals from the general population, no associations between exposure and outcome were found in the samples as a whole. However, age and gender stratified analyses showed a significant two-fold excess risk of AMI associated with SMI in women younger than 45 years of age.

**Objective 2: 'To explore the intervention receipts, outcome of inpatient mortality or recurrence following the first acute myocardial infarction among patients with serious mental illness'**

Comparing outcomes following AMI between people with a previous history of SMI (cases) and those without such a history (controls), the hypotheses were as follows:

(1) Diagnostic catheterization will be lower in cases compared to controls.

*Summary of key findings*:

This hypothesis was fully supported. People with SMI (case cohort) were less than half as likely to receive catheterization compared to controls (odds ratios (OR)= 0.37 and 0.38 in fully adjusted model for individuals with schizophrenia and bipolar disorder, respectively).

(2) Receipt of revascularization will be lower in cases compared to controls.

*Summary of key findings*:

This hypothesis was fully supported. People with SMI (case cohort) were less than half as likely (OR=0.35 and 0.47 in fully adjusted model for individuals with schizophrenia and bipolar disorder, respectively) to receive revascularization compared to controls.

(4) Receipt of revascularization after catheterization will be lower in cases compared to controls.

*Summary of key findings*:

This hypothesis was partly supported. The odds of receiving revascularization after catheterization were 0.59~0.68 times lower in people with serious mental illness than the general population, but this difference did not reach statistical significance.

(5) Inpatient complications following acute myocardial infarction will be higher in cases compared to controls.

*Summary of key findings*:

This hypothesis was not supported. Prevalences of inpatient complications following an AMI were not significantly higher in people with serious mental illness, except for respiratory failure in people with schizophrenia.

(6) The 30-day inpatient mortality following an AMI will be higher in cases compared to controls.

*Summary of key findings*:

This hypothesis was partly supported. The 30-day inpatient mortality following an acute myocardial infarction was 2.68 times significantly higher in people with schizophrenia compared to controls, but was not significantly higher in people with bipolar disorder.

(7) Recurrence of AMI within and after one year following discharge will be higher in cases compared to controls.

*Summary of key findings*:

This hypothesis was not supported. The odds of re-admissions due to a second AMI after one month or after a year following discharge were not significantly higher in people with serious mental illness in the fully adjusted model.

(8) Hospitalizations due to other cardiovascular diseases within and after a year after

discharge will be higher in cases compared to controls.

*Summary of key findings*:

This hypothesis was only partly supported. Odds of hospitalizations due to other cardiovascular diseases within and after a year following discharge were not significantly higher in people with serious mental illness in the fully adjusted model, except for hospitalization due to new onset of cardiogenic shock in people with schizophrenia and people with bipolar disorder.

**Objective 3: 'To investigate the associations between acute myocardial infarction and recent antipsychotic use among people with serious mental illness'**

Comparing a more recent (case) with a more distant (control) time period in people with serious mental illness who experienced an acute myocardial infarction, the hypotheses were as follows:

(1) Antipsychotic exposure will be more common in the case time period compared to the control time period.

*Summary of key findings*:

This hypothesis was partly supported. Recent antipsychotic exposure before the occurrence of index AMI episode was found to be more common in people with schizophrenia, but not in people with bipolar disorder. However, the association was significant for both disorders when the case period was compared with a control period 12 months previously. The association in schizophrenia was further modified by gender and prior cardiovascular diagnoses.

(2) The average dose of antipsychotic will be higher in the case period compared to the control period.

*Summary of key findings*:

Contrary to the hypothesis, the average dose of antipsychotic prescription was not significantly higher in the case period, either in people with schizophrenia or bipolar disorder. Trends suggesting a dose-dependent relationship were also not observed.

(3) Use of typical antipsychotic will be more common in the case period compared to the control period.

*Summary of key findings*:

This hypothesis was partly supported in people with schizophrenia, but not in people with bipolar disorder. The result showed that typical antipsychotic agents were prescribed more often in the case period than in the control period.

## 10.2 Summary of core methodological issues

### 10.2.1 Key strengths of this study

Taking the advantage of this large, population-based sample, the research described in this thesis possessed sufficient statistical power - an important methodological challenge in studies of serious mental illness and AMI because of the difficulties encountered in many settings in obtaining numbers large enough to draw meaningful results. In addition, this thesis analysed nationally-representative data with the high generalisability of a naturalistic clinical environment.

### 10.2.2 Methodological considerations

The main methodological limitations are considered below under the headings of chance, bias, and confounding as potential alternative explanations for observed findings.

*Chance*

Results that are statistically significant (i.e. applying the conventional definition of a p-value less than 0.05) indicated an acceptably low risk of *Type I error,* (also known as a false rejection of the null hypothesis, or a 'false-positive' finding) (Stewart, 2008). However, this assumption concerns an association between a single primary exposure and outcome, and the possibility of *Type I error* should still be borne in mind when considering multiple and secondary or subgroup analyses. For instance, in **Chapter 7,** the positive association between SMI and increased risk of AMI found in the subgroup of young women might have arisen by chance, although this subgroup analysis was planned *a priori,* based on an assumption age and gender might have modifying effects on the association of interest. The pattern of stronger associations in younger people was also observed consistently across the age range

of the sample, rather than being confined to a single subgroup which reduces the likelihood of this error. The multiple outcomes investigated in **Chapter 8** would increase the chance of *Type I error***,** although these were again conducted based on a logical, *a priori* approach to consequences of post-AMI care. In **Chapter 9**, stratified analyses were exploratory but kept to a relatively small number, and interaction tests were examined rather than just reporting significant findings within a subgroup.

*Type II error* describes the incorrect acceptance of a null hypothesis (i.e. a 'false-negative' finding) and may arise either because of a lack of statistical power or measurement error. Lack of statistical power can be considered in relation to the relatively small numbers of AMI instances in younger age groups investigated in **Chapter 7**, some of the more rare outcomes in **Chapter 8**, and possibly the null association between more recent antipsychotic use and AMI among people with bipolar disorder described in **Chapter 9**. In this respect, a *post hoc* power analysis calculated using the PS program (Dupont, 1992) showed a required number of 500 case patients needed in order to achieve a 70% power with an alpha (probability of Type 1 error) of 0.05.

*Bias*

As discussed in the previous chapters, there are potentially important considerations regarding selection bias. The first concerns the potential misclassification of true cases (patients with SMI), because the study sample was drawn from an administrative dataset without validated interviews and the application of research diagnostic criteria. Second, people with AMI who died outside a hospital would not have been captured as having outcome events in **Chapter 9** and would not have been included in the samples analysed in **Chapters 10 and 11**. Third, the sample size of

the bipolar group was relatively small and cautions should be taken when generalising the results due to the hierarchical classification algorithm applied as well as any misdiagnosis of cases as unipolar depression. Fourth, the majority of the case cohorts examined were individuals with SMI who had received hospitalization in mental health units, thus the generalisability may be limited to people more severely affected by these diagnoses. The effect of this particular selection process on findings of interest is difficult to predict; on the one hand, those with more severe symptomatology may be at higher risk of adverse outcomes because of effects of acute illness; on the other hand, they would have received more medical contact than those less well recognised and the latter group might have more negative symptomatology and poorer outcomes due to self-neglect. Fifth, in terms of information bias, although recall bias would not be an issue, patients' medical records were only available within a specified time window and it was not possible to assume that the index AMI was the first occurrence; neither was it possible to consider past psychiatric history or the duration of each mental disorder of interest though efforts were made in sensitivity analyses to address this.

*Confounding*

As described previously, although basic demographic characteristics (such as gender, age, levels of income and urbanization of residence) and previous diagnosed cardiovascular risk factors could be obtained and investigated as covariates, other information relevant to vascular risk (such as smoking status, physical activity, obesity, and psychosocial factors) was not available in this routine administrative record. Thus, the possibility of residual confounding still remains. For instance, in **Chapter 7**, although unmeasured, it is possible that the higher prevalence of cigarette smoking and unhealthy lifestyles among young women with SMI in Taiwan (Liao, 2002) might be responsible for the observed positive association. Similarly, of

relevance to findings in **Chapter 8,** previous research has discussed the possibility of medical professionals' reluctance to offer some post-AMI procedures to smokers due to concerns about potential adverse effects of cigarette smoking on post-operative care (Daumit et al., 2006; Kisely et al., 2009; Mallik et al., 2005; McDonald et al., 2003). The possible effects of these unhealthy lifestyle factors on the decision-making process of medical personnel should therefore be considered when interpreting findings. Another key confounder might be patients' actual cognitive function and their ability to express opinions or to comprehend instructions during hospitalization following AMI. This might explain some of the worse outcomes for patients with schizophrenia compared to those with bipolar disorder. Finally, in **Chapter 9**, the effects of unmeasured personal characteristics as confounders were not as influential as in **Chapters 8 and 9** because comparisons were made between two different time periods within the same individual. However, it is still important to bear in mind that there are other possible time-varying confounders that might account for the associations of interest but which could not be measured from the data available. Of particular importance is the remaining question of whether it is antipsychotic agents or the symptoms or behaviours being treated which are responsible for an apparent raised short-term risk of AMI.

## 10.3 Summary of issues that cut across three result chapters

### 10.3.1 Components of disadvantage

Although cardiovascular mortality is higher in people with SMI in Taiwan compared to controls (Chen WJ et al., 1996; Chen YH et al., 2010), findings for risk of AMI incidence in this study did not explain this for schizophrenia, apart from the relatively rare occurrence in young women, and were complex for bipolar disorder, highly dependent on other factors included in regression models. However, as discussed in **Chapter 7**, the incident AMI in this study only reflected recognized and hospitalized AMI and thus this risk might have been underestimated. On the other hand, people with SMI were found to be less likely to receive invasive coronary interventions; and for schizophrenia at least, inpatient mortality was higher. From these findings, it is possible that the higher risk of an end-point such as mortality is more explained (in Taiwan at least) by less adequate care (or possibly sudden non-hospitalized AMI) rather than AMI incidence itself. A recently reported Australian investigation of cancer outcomes in SMI appeared to draw similar conclusions – i.e. that higher cancer mortality was not due to higher overall cancer incidence but to delayed presentation and less adequate intervention(Kisely, Crowe, et al., 2012). On the other hand, findings reported in **Chapter 9** were consistent with a role of antipsychotic agents, within schizophrenia at least, as a short-term precipitant.

### 10.3.2 Differences between mental disorders

A second common finding concerned differences between schizophrenia and bipolar disorder. These were not always observed: for example, the reduced odds of intervention receipt in both mental disorders. However, there were several differences in other findings. First, as stated in **Chapter 7**, although in both mental disorders, the excess risk of AMI was higher in women less than 45 years of age,

such risk association disappeared in young women with bipolar disorder in the sensitivity analysis when early AMI was excluded. Second, despite having similarly increased odds of developing cardiovascular complications, the 30-day inpatient mortality following the index AMI was significantly higher in patients with schizophrenia, whereas no significant difference between those with bipolar disorder and the comparison group was found. Third, as described in **Chapter 9**, associations between AMI and recent antipsychotic exposure was found in people with schizophrenia but was not present for bipolar disorder in the primary analyses. The aforementioned differences between two mental disorders might reflect again the degree of health disadvantage is more severe in people with schizophrenia. Although interpretation should be made with caution due to the much smaller sample size in bipolar disorder, it would be worth investigating whether differences in disease presentation during the acute psychotic episode or patterns and strategies of antipsychotic initiation are the potential factors for the disparity, both in associations with antipsychotic exposure and in post-AMI outcome.

### 10.3.3 Acute and chronic risk effects with different causal pathways

The results from **Chapter 7** where young women with SMI were found to have elevated risk of AMI, can be contrasted with those from **Chapter 9** where recent antipsychotic exposure was associated with AMI particularly in male patients with schizophrenia without previous cardiovascular risk factors. One possible explanation is that the risk of AMI, at least in people with schizophrenia, is mediated through different causal pathways with respect to short-term and long-term risks. Interactions of disease severity, behavioral disruptions, drug compliance, identification of underlying cardiovascular risk factors, with physicians' prescription patterns between genders should also be considered.

## 10.4 Implications

### 10.4.1 Public health implications

As discussed in previous chapters, the raised risk of AMI in young women with schizophrenia and bipolar disorder could only be partially explained by demographic characteristics and cardiovascular comorbidities. Although derived from subgroup analyses, the worrying pronounced increase in AMI risk in young women is relevant from a public health perspective because health education, encouragements of changes in lifestyle might be indicated, or as evidence suggests, a reduction in the prevalence and impact of cardiovascular risk factors through offering advice and/or information for health promotion alongside recovery-focused support from mental health nurses (Hardy et al., 2012; Tosh et al., 2011). Potentially relevant in this respect, a recent study concluded that the legally framed 'community treatment orders' in Western Australia (under which, patients with serious mental illness are required to accept psychiatric treatments) were able to reduce mortality from physical causes such as cancer, cardiovascular, and central nervous system disorders through increasing contacts to health services or better access to medical resources in patients with mental illness (Kisely, Preston, et al., 2012).

With respect to the elevated inpatient mortality after AMI in schizophrenia, and decreased odds of intervention receipts following an AMI, although it is not possible to control the occurrence of misfortune or prevent all environmental stressors, health inequity threatening the physical health of people with SMI should be minimized. Policy implications should be considered with respect to legal frameworks around the decision-making process of treatment administration, promoting equality in physical healthcare for people with chronic severe mental disorders. Educational programmes to raise the awareness in medical personnel of underlying disadvantages among people with serious mental disorders should also be considered and evaluated.

### 10.4.2 Clinical implications

As well as public health interventions to improve cardiovascular risk factors at a population level and increase awareness of health inequalities, there are other potentially more direct implications for clinical services. Considering results from **Chapter 7**, it is important to bear in mind that the finding of no increased risk of AMI in this study might have arisen through under-detection or under-referral for physical disorders in people with SMI in Taiwan. Thus, there remains a need to provide equal access to cardiovascular screening (Osborn et al., 2003; Pitman et al., 2011; Osborn et al., 2011) and relevant treatments to people with SMI in order to prevent excess incidence of AMI.

The finding that patients with either mental disorder were half as likely to receive catheterization or revascularization procedures following the index AMI is clearly concerning, particularly considering that the Taiwan health system is a relatively accessible and un-rationed healthcare system. Although it is possible that there are reasons beyond anyone's control why these standard procedures were not feasible, the decision-making process of medical personnel still merits further consideration. If the reasons for low intervention receipt include refusal of treatment from people with serious mental illness or their family, medical personnel may still need to consider how they address and discuss the contents of the intervention process and prognosis. In particular, they should consider strategies for people with these mental disorders, employing more effective communications and a more humanistic approach. Specific measures might included maintaining patients' engagement in receiving medical care, better understanding of clients' and caregivers' situations or concerns, provision of emotional support, working with existing strengths, and conveying hope for the long-term (Bellack, 2006; Browne et al., 2008; Eldridge et al.,

2011; Horsfall et al., 2010). Attitudes toward specific treatment and whether all the relevant information has been revealed and contemplated sufficiently by patients or their families should all be taken into consideration, especially when previous literature has demonstrated great success in providing health services when incorporating the participation of clinicians and family members (Dixon, 1999b).

Another method to reduce barriers of access to medical care in patients with SMI might be to enhance collaborations between mental health services and primary care. Previous research has suggested that improved receipt of preventive measures, fewer visits to emergency departments, and greater improvement in quality and outcomes of medical care can be achieved by more closely integrating mental health and primary care (Druss, 2001b; Dombrovski, 2004; Pincus, 2003). Additional benefits have been derived from training psychiatrists to provide primary medical care (Dobscha, 2001), and from building 'collaborative models of care' which introduce internal or family medicine clinicians to mental health clinics or inpatient units (Silberman, 1999). Such collaborations or information changes (Horvitz-Lennon et al., 2006) to bridge the gap between general medicine and services more typically received by patients with SMI are currently lacking in the health care system in Taiwan and thus might be a future direction to work on.

Since undetected medical comorbidities occurring during hospitalizations (Cradock-O'Leary et al., 2002; Daumit, 2006) might be a reason for the elevated inpatient mortality in schizophrenia which was not fully explained by decreased likelihood of intervention receipt, it is important that medical personnel i) are more aware of potential underlying communication difficulties, ii) evaluate patients with SMI on regular basis (Laursen, 2009), iii) use specific monitoring equipment (Eldridge et al., 2011), and iv) pay more attention to the early identification of

potential disease signs, perhaps particularly in the context of active psychotic symptoms or where medically indicated treatments are refused. In addition, principles of remaining 'ALERT' when assessing patients with SMI highlighted by The Royal College of Psychiatrists in the UK have also been suggested (Hardy et al, 2012). The five priorities of 'ALERT' (The Royal College of Psychiatrists, 2009) are as follows:

• **A**wareness of the link between physical and mental health

• **L**iaison mental health services in all general hospitals

• **E**ngaging patients and carers in health services

• **R**e-organization, commissioning, and quality standards (e.g. liaison mental health services should be commissioned and reviewed against agreed specific service standards).

• **T**raining and education for all health-care professionals.

An implication for mental health services, related to findings from **Chapter 9** in particular, is that medical personnel should be cautious in considering cardiovascular side effects or early pre-AMI symptomatology when initiating antipsychotic treatment, especially in men with schizophrenia. Moreover, as discussed in the same chapter, the finding of a stronger association between AMI and recent antipsychotic exposure in the group with no previous cardiovascular risk factors also suggests a need for more rigorous medical attention to identify risk profiles for AMI among people with serious mental illness, potentially moving beyond simply asking about known diagnoses.

### 10.4.3 Research implications

Regarding the main result in **Chapter 7** where elevated risk of AMI was found in young women with schizophrenia or bipolar disorder, future investigations need to

focus on clarifying causal pathways, particularly focusing on gender differences in people with severe mental disorders within these age ranges. An example of this might be the potential increase in hypercoagulability in women with SMI who use contraceptive pills and/or who are current smokers (Daumit, 2006). Given the recognised increased risk of cardiovascular mortality and substantially reduced life expectancy in people with major mental disorders, research is also required into how much this is accounted for by AMI risk and incidence and how much by subsequent interventions received by people with mental disorders who experience an AMI.

As discussed in **Chapter 8**, the clear excess of inpatient mortality during AMI episodes in patients with schizophrenia but not bipolar disorder despite similar complication rates during hospitalization suggests that psychotic disorders should not be combined for analyses in this area. Further research exploring underlying reasons for these differences in outcome between patients with schizophrenia and bipolar disorder may need to be conducted. On the other hand, given the substantially reduced life expectancy in people with major mental disorders, research also suggests a need to understand further the clinical interactions and relationships between patients, their caregivers, and medical providers. For example, previous qualitative studies found that conceptualisations of stroke illness and ageing, socio-economic factors, resource allocation, and information provision were main themes affecting inequity in stroke care (Mold, 2003). Also, process-typed, qualitative research has explored the interface at clinical level, such as how the motivation, attitudes, and expectations to treat AMI in people with SMI among health care professionals might be influenced (Becker & Kaufman, 1995; Pound & Ebrahim 1997). Likewise, there is a need for better understanding of interactions with patient themselves and how conceptualizations may interact and affect the delivery and receipt of health services (Mold, 2003).

As mentioned previously in **Chapter 4** and discussed in **Chapter 9**, from the literature to date, this is the first study to investigate the association between AMI and recent antipsychotic exposure in SMI, applying a case-crossover design. What this method tests are essentially short-term precipitating actions related to the exposure, rather than long term risk, which should be borne in mind when interpreting results. Although it is still too early to draw conclusions about changes in antipsychotic treatment guidelines, the primary association in schizophrenia still supports a need for further investigation of potential risk effects and close monitoring of patients particularly during antipsychotic initiation. As well as this, potential thrombotic effects (Parker, 2010), and other physical changes during the psychotic state still warrant future exploration, such as dehydration, immobility, or increased cigarette smoking, which in turn might cause a pro-inflammatory response, platelet aggregation, or vessel spasm (Hagg & Spigset, 2002; Zornberg & Jick, 2000), leading to AMI in addition to any short-term effects of antipsychotic medication. Finally, the modifying factors identified (gender, diagnosis, cardiovascular risk and previous antipsychotic use) support the development and evaluation of personalized risk prediction models as well as providing potential avenues for further investigation of causal pathways.

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# APPENDICES

## Appendix 1 Detailed lists of data files applied from the NHIRD

| The following application lists of compact discs are based on the information provided from the website of NHIRD (http://www.nhri.org.tw/nhird) | | | |
|---|---|---|---|
| **Year of the data the disc contained** | **Serial number of the compact disc that contained data** | **Name of the file (in Mandrin)** | **English description of the file** |
| *Psychiatric Inpatients Medical Claim Dataset (PIMC)* | | | |
| 1996 | TN85PSY01 | 精神疾病病患_門診處方及治療明細檔,精神疾病病患_住院醫療費用清單明細檔 | Psychiatric Ambulatory care (as the **'CD'** files mentioned in chapter 6) expenditures by visits, prescriptions and treatment files |
| 1997 | TN86PSY01 | 精神疾病病患_門診處方及治療明細檔,精神疾病病患_門診處方醫令明細檔 | Psychiatric Ambulatory care expenditures by visits prescriptions and treatment files |
| 1997 | TN86PSY02 | 精神疾病病患_門診處方及治療明細檔,精神疾病病患_門診處方醫令明細檔 | Psychiatric Ambulatory care expenditures by visits prescriptions and treatment files |
| 1997 | TN86PSY03 | 精神疾病病患_門診處方及治療明細檔,精神疾病病患_門診處方醫令明細檔 | Psychiatric Ambulatory care expenditures by visits prescriptions and treatment files |
| 1997 | TN86PSY04 | 精神疾病病患_住院醫療費用清單明細檔,精神疾病病患_住院醫療費用醫令清單明細檔 | Profiles of psychiatric patients (as the '**ID**' file mentioned in chapter 6), psychiatric Inpatient expenditures (as the **'DD'** files mentioned in chapter 6) by admissions, prescriptions and treatment files |
| 1998 | TN87PSY01 | 精神疾病病患_門診處方及治療明細檔,精神疾病病患_門診處方醫令明細檔 | Psychiatric Ambulatory care expenditures by visits prescriptions and treatment files |
| 1998 | TN87PSY02 | 精神疾病病患_門診處方及治療明細檔,精神疾病病患_門診處方醫令明細檔 | Psychiatric Ambulatory care expenditures by visits prescriptions and treatment files |
| 1998 | TN87PSY03 | 精神疾病病患_門診處方及治療明細檔,精神疾病病患_門診處方醫令明細檔 | Psychiatric Ambulatory care expenditures by visits prescriptions and treatment files |

| | | | |
|---|---|---|---|
| 1998 | TN87PSY04 | 精神疾病病患 住院醫療費用清單明細檔，精神疾病病患 住院醫療費用醫令清單明細檔 | Profiles of psychiatric patients, psychiatric Inpatient expenditures by admissions, prescriptions and treatment files |
| 1999 | TN88PSY01 | 精神疾病病患 門診處方及治療明細檔，精神疾病病患 門診處方醫令明細檔 | Psychiatric Ambulatory care expenditures by visits prescriptions and treatment files |
| 1999 | TN88PSY02 | 精神疾病病患 門診處方及治療明細檔，精神疾病病患 門診處方醫令明細檔 | Psychiatric Ambulatory care expenditures by visits prescriptions and treatment files |
| 1999 | TN88PSY03 | 精神疾病病患 門診處方及治療明細檔，精神疾病病患 門診處方醫令明細檔 | Psychiatric Ambulatory care expenditures by visits prescriptions and treatment files |
| 1999 | TN88PSY04 | 精神疾病病患 門診處方及治療明細檔，精神疾病病患 門診處方醫令明細檔 | Psychiatric Ambulatory care expenditures by visits prescriptions and treatment files |
| 1999 | TN88PSY05 | 精神疾病病患 住院醫療費用清單明細檔，精神疾病病患 住院醫療費用醫令清單明細檔 | Profiles of psychiatric patients, psychiatric Inpatient expenditures by admissions, prescriptions and treatment files |
| 2000 | TN89PSY01 | 精神疾病病患 門診處方及治療明細檔，精神疾病病患 門診處方醫令明細檔 | Psychiatric Ambulatory care expenditures by visits prescriptions and treatment files |
| 2000 | TN89PSY02 | 精神疾病病患 門診處方及治療明細檔，精神疾病病患 門診處方醫令明細檔 | Psychiatric Ambulatory care expenditures by visits prescriptions and treatment files |
| 2000 | TN89PSY03 | 精神疾病病患 門診處方及治療明細檔，精神疾病病患 門診處方醫令明細檔 | Psychiatric Ambulatory care expenditures by visits prescriptions and treatment files |
| 2000 | TN89PSY04 | 精神疾病病患 住院醫療費用清單明細檔 | Profiles of psychiatric patients, psychiatric Inpatient expenditures by admissions files |
| 2000 | TN89PSY05 | 精神疾病病患 住院醫療費用醫令清單明細檔 | Psychiatric inpatient prescriptions and treatment files |
| 2001 | TN90PSY01 | 精神疾病病患 門診處方及治療明細檔，精神疾病病患 門診處方醫令明細檔 | Psychiatric Ambulatory care expenditures by visits prescriptions and treatment files |
| 2001 | TN90PSY02 | 精神疾病病患 門診處方及治療明細檔，精神疾病病患 門診處方醫令 | Psychiatric Ambulatory care expenditures by visits prescriptions |

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| | | 明細檔 | and treatment files |
| 2001 | TN90PSY03 | 精神疾病病患 門診處方及治療明細檔，精神疾病病患 門診處方醫令明細檔 | Psychiatric Ambulatory care expenditures by visits prescriptions and treatment files |
| 2001 | TN90PSY04 | 精神疾病病患 住院醫療費用清單明細檔 | Profiles of psychiatric patients, psychiatric Inpatient expenditures by admissions files |
| 2001 | TN90PSY05 | 精神疾病病患 住院醫療費用醫令清單明細檔 | Psychiatric inpatient prescriptions and treatment files |
| 2001 | TN90PSY06 | 精神疾病病患 住院醫療費用醫令清單明細檔 | Psychiatric inpatient prescriptions and treatment files |
| 2002 | TN91PSY01 | 精神疾病病患 門診處方及治療明細檔，精神疾病病患 門診處方醫令明細檔 | Psychiatric Ambulatory care expenditures by visits prescriptions and treatment files |
| 2002 | TN91PSY02 | 精神疾病病患 門診處方及治療明細檔，精神疾病病患 門診處方醫令明細檔 | Psychiatric Ambulatory care expenditures by visits prescriptions and treatment files |
| 2002 | TN91PSY03 | 精神疾病病患 門診處方及治療明細檔，精神疾病病患 門診處方醫令明細檔 | Psychiatric Ambulatory care expenditures by visits prescriptions and treatment files |
| 2002 | TN91PSY04 | 精神疾病病患 住院醫療費用清單明細檔 | Psychiatric Inpatient expenditures by admissions files |
| 2002 | TN91PSY05 | 精神疾病病患 住院醫療費用醫令清單明細檔，精神疾病病患 承保資料 | Profiles of psychiatric patients, psychiatric inpatient prescriptions and treatment files |
| 2003 | TN92PSY01 | 精神疾病病患 門診處方及治療明細檔，精神疾病病患 門診處方醫令明細檔 | Psychiatric Ambulatory care expenditures by visits prescriptions and treatment files |
| 2003 | TN92PSY02 | 精神疾病病患 門診處方及治療明細檔，精神疾病病患 門診處方醫令明細檔 | Psychiatric Ambulatory care expenditures by visits prescriptions and treatment files |
| 2003 | TN92PSY03 | 精神疾病病患 門診處方及治療明細檔，精神疾病病患 門診處方醫令明細檔 | Psychiatric Ambulatory care expenditures by visits prescriptions and treatment files |
| 2003 | TN92PSY04 | 精神疾病病患 住院醫療費用清單明細檔，精神疾病病患 住院醫療費用醫令清單明細檔，精神疾病病患 承保資料 | Profiles of psychiatric patients, psychiatric Inpatient expenditures by admissions, prescriptions and treatment files |

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| 2004 | TN93PSY01 | 精神疾病病患 門診處方及治療明細檔，精神疾病病患 門診處方醫令明細檔 | Psychiatric Ambulatory care expenditures by visits prescriptions and treatment files |
| 2004 | TN93PSY02 | 精神疾病病患 門診處方及治療明細檔，精神疾病病患 門診處方醫令明細檔 | Psychiatric Ambulatory care expenditures by visits prescriptions and treatment files |
| 2004 | TN93PSY03 | 精神疾病病患 門診處方及治療明細檔，精神疾病病患 門診處方醫令明細檔 | Psychiatric Ambulatory care expenditures by visits prescriptions and treatment files |
| 2004 | TN93PSY04 | 精神疾病病患 住院醫療費用清單明細檔，精神疾病病患 住院醫療費用醫令清單明細檔，精神疾病病患 承保資料 | Profiles of psychiatric patients, psychiatric Inpatient expenditures by admissions, prescriptions and treatment files |
| 2005 | TN94PSY01 | 精神疾病病患 門診處方及治療明細檔，精神疾病病患 門診處方醫令明細檔 | Psychiatric Ambulatory care expenditures by visits prescriptions and treatment files |
| 2005 | TN94PSY02 | 精神疾病病患 門診處方及治療明細檔，精神疾病病患 門診處方醫令明細檔 | Psychiatric Ambulatory care expenditures by visits prescriptions and treatment files |
| 2005 | TN94PSY03 | 精神疾病病患 門診處方及治療明細檔，精神疾病病患 門診處方醫令明細檔 | Psychiatric Ambulatory care expenditures by visits prescriptions and treatment files |
| 2005 | TN94PSY04 | 精神疾病病患 住院醫療費用清單明細檔，精神疾病病患 住院醫療費用醫令清單明細檔，精神疾病病患 承保資料 | Profiles of psychiatric patients, psychiatric Inpatient expenditures by admissions, prescriptions and treatment files |
| 2006 | TN95PSY01 | 精神疾病病患 門診處方及治療明細檔，精神疾病病患 門診處方醫令明細檔 | Psychiatric Ambulatory care expenditures by visits prescriptions and treatment files |
| 2006 | TN95PSY02 | 精神疾病病患 門診處方及治療明細檔，精神疾病病患 門診處方醫令明細檔 | Psychiatric Ambulatory care expenditures by visits prescriptions and treatment files |
| 2006 | TN95PSY03 | 精神疾病病患 門診處方及治療明細檔，精神疾病病患 門診處方醫令明細檔 | Psychiatric Ambulatory care expenditures by visits prescriptions and treatment files |
| 2006 | TN95PSY04 | 精神疾病病患 住院醫療費用清單明細檔，精神疾病病患 住院醫療費用醫令清單明細檔，精神疾病病患 承保資料 | Profiles of psychiatric patients, psychiatric Inpatient expenditures by admissions, prescriptions and treatment files |

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| 2007 | TN96PSY01 | 精神疾病病患 門診處方及治療明細檔，精神疾病病患 門診處方醫令明細檔 | Psychiatric Ambulatory care expenditures by visits prescriptions and treatment files |
| 2007 | TN96PSY02 | 精神疾病病患 門診處方及治療明細檔，精神疾病病患 門診處方醫令明細檔 | Psychiatric Ambulatory care expenditures by visits prescriptions and treatment files |
| 2007 | TN96PSY03 | 精神疾病病患 門診處方及治療明細檔，精神疾病病患 門診處方醫令明細檔 | Psychiatric Ambulatory care expenditures by visits prescriptions and treatment files |
| 2007 | TN96PSY04 | 精神疾病病患 住院醫療費用清單明細檔，精神疾病病患 住院醫療費用醫令清單明細檔，精神疾病病患 承保資料 | Profiles of psychiatric patients, psychiatric Inpatient expenditures by admissions, prescriptions and treatment files |
| *Longitudinal Health Insurance Research Database 2000 (LHID)* | | | |
| 1996 | RN10_1996 | 承保資料，門診處方及治療明細檔，住院醫療費用清單明細檔，特約藥局處方及調劑明細檔 | Patient profiles (as the **'ID'** files mentioned in chapter 6), Ambulatory care (as the **'CD'** files mentioned in chapter 6) expenditures by visits prescriptions and treatments, Inpatient expenditures by admissions files, Prescription files |
| 1997 | RN10_1997 | 門診處方及治療明細檔，門診處方醫令明細檔，住院醫療費用清單明細檔，住院醫療費用醫令清單明細檔，特約藥局處方及調劑明細檔，特約藥局處方調劑醫令 | Patient profiles, Ambulatory care expenditures by visits prescriptions and treatments, Inpatient expenditures by admissions, prescriptions and treatment files |
| 1998 | RN10_1998 | 門診處方及治療明細檔，門診處方醫令明細檔，住院醫療費用清單明細檔，住院醫療費用醫令清單明細檔，特約藥局處方及調劑明細檔，特約藥局處方調劑醫令 | Patient profiles , Ambulatory care expenditures by visits prescriptions and treatments, Inpatient expenditures by admissions, prescriptions and treatment files |
| 1999 | RN10_1999_1 | 門診處方及治療明細檔，住院醫療費用清單明細檔，特約藥局處方及調劑明細檔，特約藥局處方調劑醫令檔 | Patient profiles, Ambulatory care expenditures by visits prescriptions and treatments, Inpatient expenditures (as the **'DD'** files mentioned in chapter 6) by admissions, prescriptions and treatment files |
| 1999 | RN10_1999_2 | 門診處方醫令明細檔 | Ambulatory care expenditures by visits prescriptions and treatments |
| 2000 | RN10_2000 | 門診處方及治療明細檔，門診處方 | Patient profiles, Ambulatory care |

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| | | 醫令明細檔，住院醫療費用清單明細檔，住院醫療費用醫令清單明細檔，特約藥局處方及調劑明細檔，特約藥局處方調劑醫令 | expenditures by visits prescriptions and treatments, Inpatient expenditures by admissions, prescriptions and treatment files |
| 2001 | RN10_2001 | 門診處方及治療明細檔，門診處方醫令明細檔，住院醫療費用清單明細檔，住院醫療費用醫令清單明細檔，特約藥局處方及調劑明細檔，特約藥局處方調劑醫令 | Patient profiles, Ambulatory care expenditures by visits prescriptions and treatments, Inpatient expenditures by admissions, prescriptions and treatment files |
| 2002 | RN10_2002 | 門診處方及治療明細檔，門診處方醫令明細檔，住院醫療費用清單明細檔，住院醫療費用醫令清單明細檔，特約藥局處方及調劑明細檔，特約藥局處方調劑醫令，承保資料 | Patient profiles, Ambulatory care expenditures by visits prescriptions and treatments, Inpatient expenditures by admissions, prescriptions and treatment files |
| 2003 | RN10_2003 | 門診處方及治療明細檔，門診處方醫令明細檔，住院醫療費用清單明細檔，住院醫療費用醫令清單明細檔，特約藥局處方及調劑明細檔，特約藥局處方調劑醫令，承保資料 | Patient profiles, Ambulatory care expenditures by visits prescriptions and treatments, Inpatient expenditures by admissions, prescriptions and treatment files |
| 2004 | RN10_2004_1 | 門診處方及治療明細檔，住院醫療費用清單明細檔，住院醫療費用醫令清單明細檔，特約藥局處方及調劑明細檔，特約藥局處方調劑醫令檔，承保資料 | Patient profiles, Ambulatory care expenditures by visits prescriptions and treatments, Inpatient expenditures by admissions, prescriptions and treatment files |
| 2004 | RN10_2004_2 | 門診處方醫令明細檔 | Ambulatory care expenditures by visits prescriptions and treatments |
| 2005 | RN10_2005_1 | 門診處方及治療明細檔，住院醫療費用清單明細檔，住院醫療費用醫令清單明細檔，特約藥局處方及調劑明細檔，特約藥局處方調劑醫令檔，承保資料 | Patient profiles, Ambulatory care expenditures by visits prescriptions and treatments, Inpatient expenditures by admissions, prescriptions and treatment files |
| 2005 | RN10_2005_2 | 門診處方醫令明細檔 | Ambulatory care expenditures by visits prescriptions and treatments |
| 2006 | RN10_2006 | 門診處方及治療明細檔，門診處方醫令明細檔，住院醫療費用清單明細檔，住院醫療費用醫令清單明細檔，特約藥局處方及調劑明細檔，特約藥局處方調劑醫令，承保資料 | Patient profiles, Ambulatory care expenditures by visits prescriptions and treatments, Inpatient expenditures by admissions, prescriptions and treatment files |
| 2007 | RN10_2007 | 門診處方及治療明細檔，門診處方醫令明細檔，住院醫療費用清單明 | Patient profiles, Ambulatory care expenditures by visits prescriptions |

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| | | 細檔，住院醫療費用醫令清單明細檔，特約藥局處方及調劑明細檔，特約藥局處方調劑醫令，承保資料 | and treatments, Inpatient expenditures by admissions, prescriptions and treatment files |
| 1996 | RN20_1996 | 承保資料，門診處方及治療明細檔，住院醫療費用清單明細檔，特約藥局處方及調劑明細檔 | Patient profiles, Ambulatory care expenditures by visits prescriptions and treatments, Inpatient expenditures by admissions, prescriptions and treatment files |
| 1997 | RN20_1997 | 門診處方及治療明細檔，門診處方醫令明細檔，住院醫療費用清單明細檔，住院醫療費用醫令清單明細檔，特約藥局處方及調劑明細檔，特約藥局處方調劑醫令 | Patient profiles, Ambulatory care expenditures by visits prescriptions and treatments, Inpatient expenditures by admissions, prescriptions and treatment files |
| 1998 | RN20_1998 | 門診處方及治療明細檔，門診處方醫令明細檔，住院醫療費用清單明細檔，住院醫療費用醫令清單明細檔，特約藥局處方及調劑明細檔，特約藥局處方調劑醫令 | Patient profiles, Ambulatory care expenditures by visits prescriptions and treatments, Inpatient expenditures by admissions, prescriptions and treatment files |
| 1999 | RN20_1999_1 | 門診處方及治療明細檔，住院醫療費用清單明細檔，住院醫療費用醫令清單明細檔，特約藥局處方及調劑明細檔，特約藥局處方調劑醫令檔 | Patient profiles, Ambulatory care expenditures by visits prescriptions and treatments, Inpatient expenditures by admissions, prescriptions and treatment files |
| 1999 | RN20_1999_2 | 門診處方醫令明細檔 | Ambulatory care expenditures by visits prescriptions and treatments |
| 2000 | RN20_2000 | 門診處方及治療明細檔，門診處方醫令明細檔，住院醫療費用清單明細檔，住院醫療費用醫令清單明細檔，特約藥局處方及調劑明細檔，特約藥局處方調劑醫令 | Patient profiles, Ambulatory care expenditures by visits prescriptions and treatments, Inpatient expenditures by admissions, prescriptions and treatment files |
| 2001 | RN20_2001 | 門診處方及治療明細檔，門診處方醫令明細檔，住院醫療費用清單明細檔，住院醫療費用醫令清單明細檔，特約藥局處方及調劑明細檔，特約藥局處方調劑醫令 | Patient profiles, Ambulatory care expenditures by visits prescriptions and treatments, Inpatient expenditures by admissions, prescriptions and treatment files |
| 2002 | RN20_2002 | 門診處方及治療明細檔，門診處方醫令明細檔，住院醫療費用清單明細檔，住院醫療費用醫令清單明細檔，特約藥局處方及調劑明細檔，特約藥局處方調劑醫令，承保資料 | Patient profiles, Ambulatory care expenditures by visits prescriptions and treatments, Inpatient expenditures by admissions, prescriptions and treatment files |

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| 2003 | RN20_2003 | 門診處方及治療明細檔，門診處方醫令明細檔，住院醫療費用清單明細檔，住院醫療費用醫令清單明細檔，特約藥局處方及調劑明細檔，特約藥局處方調劑醫令，承保資料 | Patient profiles, Ambulatory care expenditures by visits prescriptions and treatments, Inpatient expenditures by admissions, prescriptions and treatment files |
| 2004 | RN20_2004_1 | 門診處方及治療明細檔，住院醫療費用清單明細檔，住院醫療費用醫令清單明細檔，特約藥局處方及調劑明細檔，特約藥局處方調劑醫令檔，承保資料 | Patient profiles, Ambulatory care expenditures by visits prescriptions and treatments, Inpatient expenditures by admissions, prescriptions and treatment files |
| 2004 | RN20_2004_2 | 門診處方醫令明細檔 | Ambulatory care expenditures by visits prescriptions and treatments |
| 2005 | RN20_2005_1 | 門診處方及治療明細檔，住院醫療費用清單明細檔，住院醫療費用醫令清單明細檔，特約藥局處方及調劑明細檔，特約藥局處方調劑醫令檔，承保資料 | Patient profiles, Ambulatory care expenditures by visits prescriptions and treatments, Inpatient expenditures by admissions, prescriptions and treatment files |
| 2005 | RN20_2005_2 | 門診處方醫令明細檔 | Patient profiles, Ambulatory care expenditures by visits prescriptions and treatments, Inpatient expenditures by admissions files, Prescription files |
| 2006 | RN20_2006 | 門診處方及治療明細檔，門診處方醫令明細檔，住院醫療費用清單明細檔，住院醫療費用醫令清單明細檔，特約藥局處方及調劑明細檔，特約藥局處方調劑醫令，承保資料 | Patient profiles, Ambulatory care expenditures by visits prescriptions and treatments, Inpatient expenditures by admissions, prescriptions and treatment files |
| 2007 | RN20_2007_1 | 門診處方及治療明細檔， 住院醫療費用清單明細檔，住院醫療費用醫令清單明細檔，特約藥局處方及調劑明細檔，特約藥局處方調劑醫令，承保資料 | Patient profiles, Ambulatory care expenditures by visits prescriptions and treatments, Inpatient expenditures by admissions, prescriptions and treatment files |
| 2007 | RN20_2007_2 | 門診處方醫令明細檔 | Ambulatory care expenditures by visits prescriptions and treatments |
| 1996 | RN01_1996 | 承保資料，門診處方及治療明細檔，住院醫療費用清單明細檔，特約藥局處方及調劑明細檔 | Patient profiles, Ambulatory care expenditures by visits prescriptions and treatments, Inpatient expenditures by admissions, prescriptions and treatment files |
| 1997 | RN01_1997 | 門診處方及治療明細檔，門診處方醫令明細檔，住院醫療費用清單明 | Patient profiles, Ambulatory care expenditures by visits prescriptions |

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| | | 細檔，住院醫療費用醫令清單明細檔，特約藥局處方及調劑明細檔，特約藥局處方調劑醫令 | and treatments, Inpatient expenditures by admissions, prescriptions and treatment files |
| 1998 | RN01_1998 | 門診處方及治療明細檔，門診處方醫令明細檔，住院醫療費用清單明細檔，住院醫療費用醫令清單明細檔，特約藥局處方及調劑明細檔，特約藥局處方調劑醫令 | Patient profiles, Ambulatory care expenditures by visits prescriptions and treatments, Inpatient expenditures by admissions, prescriptions and treatment files |
| 1999 | RN01_1999_1 | 門診處方及治療明細檔，住院醫療費用清單明細檔，特約藥局處方及調劑明細檔，特約藥局處方調劑醫令檔 | Patient profiles, Ambulatory care expenditures by visits prescriptions and treatments, Inpatient expenditures by admissions, prescriptions and treatment files |
| 1999 | RN01_1999_2 | 門診處方醫令明細檔 | Ambulatory care expenditures by visits prescriptions and treatments |
| 2000 | RN01_2000 | 門診處方及治療明細檔，門診處方醫令明細檔，住院醫療費用清單明細檔，住院醫療費用醫令清單明細檔，特約藥局處方及調劑明細檔，特約藥局處方調劑醫令 | Patient profiles, Ambulatory care expenditures by visits prescriptions and treatments, Inpatient expenditures by admissions, prescriptions and treatment files |
| 2001 | RN01_2001 | 門診處方及治療明細檔，門診處方醫令明細檔，住院醫療費用清單明細檔，住院醫療費用醫令清單明細檔，特約藥局處方及調劑明細檔，特約藥局處方調劑醫令 | Patient profiles, Ambulatory care expenditures by visits prescriptions and treatments, Inpatient expenditures by admissions, prescriptions and treatment files |
| 2002 | RN01_2002 | 門診處方及治療明細檔，門診處方醫令明細檔，住院醫療費用清單明細檔，住院醫療費用醫令清單明細檔，特約藥局處方及調劑明細檔，特約藥局處方調劑醫令，承保資料 | Patient profiles, Ambulatory care expenditures by visits prescriptions and treatments, Inpatient expenditures by admissions, prescriptions and treatment files |
| 2003 | RN01_2003 | 門診處方及治療明細檔，門診處方醫令明細檔，住院醫療費用清單明細檔，住院醫療費用醫令清單明細檔，特約藥局處方及調劑明細檔，特約藥局處方調劑醫令，承保資料 | Patient profiles, Ambulatory care expenditures by visits prescriptions and treatments, Inpatient expenditures by admissions files, Prescription files |
| 2004 | RN01_2004_1 | 門診處方及治療明細檔，住院醫療費用清單明細檔，住院醫療費用醫令清單明細檔，特約藥局處方及調劑明細檔，特約藥局處方調劑醫令檔，承保資料 | Patient profiles, Ambulatory care expenditures by visits prescriptions and treatments, Inpatient expenditures by admissions files, Prescription files |

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| 2004 | RN01_2004_2 | 門診處方醫令明細檔 | Ambulatory care expenditures by visits prescriptions and treatments |
| 2005 | RN01_2005_1 | 門診處方及治療明細檔，住院醫療費用清單明細檔，住院醫療費用醫令清單明細檔，特約藥局處方及調劑明細檔，特約藥局處方調劑醫令檔，承保資料 | Patient profiles, Ambulatory care expenditures by visits prescriptions and treatments, Inpatient expenditures by admissions, prescriptions and treatment files |
| 2005 | RN01_2005_2 | 門診處方醫令明細檔 | Ambulatory care expenditures by visits prescriptions and treatments |
| 2006 | RN01_2006 | 門診處方及治療明細檔，門診處方醫令明細檔，住院醫療費用清單明細檔，住院醫療費用醫令清單明細檔，特約藥局處方及調劑明細檔，特約藥局處方調劑醫令，承保資料 | Patient profiles, Ambulatory care expenditures by visits prescriptions and treatments, Inpatient expenditures by admissions, prescriptions and treatment files |
| 2007 | RN01_2007 | 門診處方及治療明細檔，門診處方醫令明細檔，住院醫療費用清單明細檔，住院醫療費用醫令清單明細檔，特約藥局處方及調劑明細檔，特約藥局處方調劑醫令，承保資料 | Patient profiles, Ambulatory care expenditures by visits prescriptions and treatments, Inpatient expenditures by admissions, prescriptions and treatment files |
| 1996 | RN06_1996 | 承保資料，門診處方及治療明細檔，住院醫療費用清單明細檔，特約藥局處方及調劑明細檔 | Patient profiles, Ambulatory care expenditures by visits prescriptions and treatments, Inpatient expenditures by admissions files, Prescription files |
| 1997 | RN06_1997 | 門診處方及治療明細檔，門診處方醫令明細檔，住院醫療費用清單明細檔，住院醫療費用醫令清單明細檔，特約藥局處方及調劑明細檔，特約藥局處方調劑醫令 | Patient profiles, Ambulatory care expenditures by visits prescriptions and treatments, Inpatient expenditures by admissions, prescriptions and treatment files |
| 1998 | RN06_1998 | 門診處方及治療明細檔，門診處方醫令明細檔，住院醫療費用清單明細檔，住院醫療費用醫令清單明細檔，特約藥局處方及調劑明細檔，特約藥局處方調劑醫令 | Patient profiles, Ambulatory care expenditures by visits prescriptions and treatments, Inpatient expenditures by admissions, prescriptions and treatment files |
| 1999 | RN06_1999_1 | 門診處方及治療明細檔，住院醫療費用清單明細檔，特約藥局處方及調劑明細檔，特約藥局處方調劑醫令檔 | Patient profiles, Ambulatory care expenditures by visits prescriptions and treatments, Inpatient expenditures by admissions, prescriptions and treatment files |
| 1999 | RN06_1999_2 | 門診處方醫令明細檔 | Ambulatory care expenditures by visits prescriptions and treatments |

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| 2000 | RN06_2000 | 門診處方及治療明細檔，門診處方醫令明細檔，住院醫療費用清單明細檔，住院醫療費用醫令清單明細檔，特約藥局處方及調劑明細檔，特約藥局處方調劑醫令 | Patient profiles, Ambulatory care expenditures by visits prescriptions and treatments, Inpatient expenditures by admissions, prescriptions and treatment files |
| 2001 | RN06_2001 | 門診處方及治療明細檔，門診處方醫令明細檔，住院醫療費用清單明細檔，住院醫療費用醫令清單明細檔，特約藥局處方及調劑明細檔，特約藥局處方調劑醫令 | Patient profiles, Ambulatory care expenditures by visits prescriptions and treatments, Inpatient expenditures by admissions, prescriptions and treatment files |
| 2002 | RN06_2002 | 門診處方及治療明細檔，門診處方醫令明細檔，住院醫療費用清單明細檔，住院醫療費用醫令清單明細檔，特約藥局處方及調劑明細檔，特約藥局處方調劑醫令，承保資料 | Patient profiles, Ambulatory care expenditures by visits prescriptions and treatments, Inpatient expenditures by admissions, prescriptions and treatment files |
| 2003 | RN06_2003 | 門診處方及治療明細檔，門診處方醫令明細檔，住院醫療費用清單明細檔，住院醫療費用醫令清單明細檔，特約藥局處方及調劑明細檔，特約藥局處方調劑醫令，承保資料 | Patient profiles, Ambulatory care expenditures by visits prescriptions and treatments, Inpatient expenditures by admissions, prescriptions and treatment files |
| 2004 | RN06_2004_1 | 門診處方及治療明細檔，住院醫療費用清單明細檔，住院醫療費用醫令清單明細檔，特約藥局處方及調劑明細檔，特約藥局處方調劑醫令檔，承保資料 | Patient profiles, Ambulatory care expenditures by visits prescriptions and treatments, Inpatient expenditures by admissions, prescriptions and treatment files |
| 2004 | RN06_2004_2 | 門診處方醫令明細檔 | Ambulatory care expenditures by visits prescriptions and treatments |
| 2005 | RN06_2005_1 | 門診處方及治療明細檔，住院醫療費用清單明細檔，住院醫療費用醫令清單明細檔，特約藥局處方及調劑明細檔，特約藥局處方調劑醫令檔，承保資料 | Patient profiles, Ambulatory care expenditures by visits prescriptions and treatments, Inpatient expenditures by admissions, prescriptions and treatment files |
| 2005 | RN06_2005_2 | 門診處方醫令明細檔 | Ambulatory care expenditures by visits prescriptions and treatments |
| 2006 | RN06_2006 | 門診處方及治療明細檔，門診處方醫令明細檔，住院醫療費用清單明細檔，住院醫療費用醫令清單明細檔，特約藥局處方及調劑明細檔，特約藥局處方調劑醫令，承保資料 | Patient profiles, Ambulatory care expenditures by visits prescriptions and treatments, Inpatient expenditures by admissions, prescriptions and treatment files |
| 2007 | RN06_2007_1 | 門診處方及治療明細檔，門診處方 | Patient profiles, Ambulatory care |

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| | | 醫令明細檔，住院醫療費用清單明細檔，住院醫療費用醫令清單明細檔，特約藥局處方及調劑明細檔，特約藥局處方調劑醫令，承保資料 | expenditures by visits prescriptions and treatments, Inpatient expenditures by admissions, prescriptions and treatment files |
| 2007 | RN06_2007_1 | 門診處方醫令明細檔 | Ambulatory care expenditures by visits prescriptions and treatments |
| 1996 | RN14_1996 | 承保資料，門診處方及治療明細檔，住院醫療費用清單明細檔，特約藥局處方及調劑明細檔 | Patient profiles, Ambulatory care expenditures by visits prescriptions and treatments, Inpatient expenditures by admissions, prescriptions and treatment files |
| 1997 | RN14_1997 | 門診處方及治療明細檔，門診處方醫令明細檔，住院醫療費用清單明細檔，住院醫療費用醫令清單明細檔，特約藥局處方及調劑明細檔，特約藥局處方調劑醫令 | Patient profiles, Ambulatory care expenditures by visits prescriptions and treatments, Inpatient expenditures by admissions, prescriptions and treatment files |
| 1998 | RN14_1998 | 門診處方及治療明細檔，門診處方醫令明細檔，住院醫療費用清單明細檔，住院醫療費用醫令清單明細檔，特約藥局處方及調劑明細檔，特約藥局處方調劑醫令 | Patient profiles, Ambulatory care expenditures by visits prescriptions and treatments, Inpatient expenditures by admissions, prescriptions and treatment files |
| 1999 | RN14_1999_1 | 門診處方及治療明細檔，住院醫療費用清單明細檔，住院醫療費用醫令清單明細檔，特約藥局處方及調劑明細檔，特約藥局處方調劑醫令檔 | Patient profiles, Ambulatory care expenditures by visits prescriptions and treatments, Inpatient expenditures by admissions, prescriptions and treatment files |
| 1999 | RN14_1999_2 | 門診處方醫令明細檔 | Ambulatory care expenditures by visits prescriptions and treatments |
| 2000 | RN14_2000 | 門診處方及治療明細檔，門診處方醫令明細檔，住院醫療費用清單明細檔，住院醫療費用醫令清單明細檔，特約藥局處方及調劑明細檔，特約藥局處方調劑醫令 | Patient profiles, Ambulatory care expenditures by visits prescriptions and treatments, Inpatient expenditures by admissions, prescriptions and treatment files |
| 2001 | RN14_2001 | 門診處方及治療明細檔，門診處方醫令明細檔，住院醫療費用清單明細檔，住院醫療費用醫令清單明細檔，特約藥局處方及調劑明細檔，特約藥局處方調劑醫令 | Patient profiles, Ambulatory care expenditures by visits prescriptions and treatments, Inpatient expenditures by admissions, prescriptions and treatment files |
| 2002 | RN14_2002 | 門診處方及治療明細檔，門診處方醫令明細檔，住院醫療費用清單明 | Patient profiles, Ambulatory care expenditures by visits prescriptions |

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| | | 細檔，住院醫療費用醫令清單明細檔，特約藥局處方及調劑明細檔，特約藥局處方調劑醫令，承保資料 | and treatments, Inpatient expenditures by admissions, prescriptions and treatment files |
| 2003 | RN14_2003 | 門診處方及治療明細檔，門診處方醫令明細檔，住院醫療費用清單明細檔，住院醫療費用醫令清單明細檔，特約藥局處方及調劑明細檔，特約藥局處方調劑醫令，承保資料 | Patient profiles, Ambulatory care expenditures by visits prescriptions and treatments, Inpatient expenditures by admissions, prescriptions and treatment files |
| 2004 | RN14_2004_1 | 門診處方及治療明細檔，住院醫療費用清單明細檔，住院醫療費用醫令清單明細檔，特約藥局處方及調劑明細檔，特約藥局處方調劑醫令檔，承保資料 | Patient profiles, Ambulatory care expenditures by visits prescriptions and treatments, Inpatient expenditures by admissions, prescriptions and treatment files |
| 2004 | RN14_2004_2 | 門診處方醫令明細檔 | Ambulatory care expenditures by visits prescriptions and treatments |
| 2005 | RN14_2005_1 | 門診處方及治療明細檔，住院醫療費用清單明細檔，住院醫療費用醫令清單明細檔，特約藥局處方及調劑明細檔，特約藥局處方調劑醫令檔，承保資料 | Patient profiles, Ambulatory care expenditures by visits prescriptions and treatments, Inpatient expenditures by admissions, prescriptions and treatment files |
| 2005 | RN14_2005_2 | 門診處方醫令明細檔 | Patient profiles, Ambulatory care expenditures by visits prescriptions and treatments, Inpatient expenditures by admissions files, Prescription files |
| 2006 | RN14_2006 | 門診處方及治療明細檔，門診處方醫令明細檔，住院醫療費用清單明細檔，住院醫療費用醫令清單明細檔，特約藥局處方及調劑明細檔，特約藥局處方調劑醫令，承保資料 | Patient profiles, Ambulatory care expenditures by visits prescriptions and treatments, Inpatient expenditures by admissions, prescriptions and treatment files |
| 2007 | RN14_2007 | 門診處方及治療明細檔， 住院醫療費用清單明細檔，住院醫療費用醫令清單明細檔，特約藥局處方及調劑明細檔，特約藥局處方調劑醫令，承保資料 | Patient profiles, Ambulatory care expenditures by visits prescriptions and treatments, Inpatient expenditures by admissions, prescriptions and treatment files |
| 1996 | RN19_1996 | 承保資料，門診處方及治療明細檔，住院醫療費用清單明細檔，特約藥局處方及調劑明細檔 | Patient profiles, Ambulatory care expenditures by visits prescriptions and treatments, Inpatient expenditures by admissions, prescriptions and treatment files |
| 1997 | RN19_1997 | 門診處方及治療明細檔，門診處方 | Patient profiles, Ambulatory care |

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| | | 醫令明細檔，住院醫療費用清單明細檔，住院醫療費用醫令清單明細檔，特約藥局處方及調劑明細檔，特約藥局處方調劑醫令 | expenditures by visits prescriptions and treatments, Inpatient expenditures by admissions, prescriptions and treatment files |
| 1998 | RN19_1998 | 門診處方及治療明細檔，門診處方醫令明細檔，住院醫療費用清單明細檔，住院醫療費用醫令清單明細檔，特約藥局處方及調劑明細檔，特約藥局處方調劑醫令 | Patient profiles, Ambulatory care expenditures by visits prescriptions and treatments, Inpatient expenditures by admissions, prescriptions and treatment files |
| 1999 | RN19_1999_1 | 門診處方及治療明細檔，住院醫療費用清單明細檔，特約藥局處方及調劑明細檔，特約藥局處方調劑醫令檔 | Patient profiles, Ambulatory care expenditures by visits prescriptions and treatments, Inpatient expenditures by admissions, prescriptions and treatment files |
| 1999 | RN19_1999_2 | 門診處方醫令明細檔 | Ambulatory care expenditures by visits prescriptions and treatments |
| 2000 | RN19_2000 | 門診處方及治療明細檔，門診處方醫令明細檔，住院醫療費用清單明細檔，住院醫療費用醫令清單明細檔，特約藥局處方及調劑明細檔，特約藥局處方調劑醫令 | Patient profiles, Ambulatory care expenditures by visits prescriptions and treatments, Inpatient expenditures by admissions, prescriptions and treatment files |
| 2001 | RN19_2001 | 門診處方及治療明細檔，門診處方醫令明細檔，住院醫療費用清單明細檔，住院醫療費用醫令清單明細檔，特約藥局處方及調劑明細檔，特約藥局處方調劑醫令 | Patient profiles, Ambulatory care expenditures by visits prescriptions and treatments, Inpatient expenditures by admissions, prescriptions and treatment files |
| 2002 | RN19_2002 | 門診處方及治療明細檔，門診處方醫令明細檔，住院醫療費用清單明細檔，住院醫療費用醫令清單明細檔，特約藥局處方及調劑明細檔，特約藥局處方調劑醫令，承保資料 | Patient profiles, Ambulatory care expenditures by visits prescriptions and treatments, Inpatient expenditures by admissions, prescriptions and treatment files |
| 2003 | RN19_2003 | 門診處方及治療明細檔，門診處方醫令明細檔，住院醫療費用清單明細檔，住院醫療費用醫令清單明細檔，特約藥局處方及調劑明細檔，特約藥局處方調劑醫令，承保資料 | Patient profiles, Ambulatory care expenditures by visits prescriptions and treatments, Inpatient expenditures by admissions files, Prescription files |
| 2004 | RN19_2004_1 | 門診處方及治療明細檔，住院醫療費用清單明細檔，住院醫療費用醫令清單明細檔，特約藥局處方及調劑明細檔，特約藥局處方調劑醫令檔，承保資料 | Patient profiles, Ambulatory care expenditures by visits prescriptions and treatments, Inpatient expenditures by admissions files, Prescription files |

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| 2004 | RN19_2004_2 | 門診處方醫令明細檔 | Ambulatory care expenditures by visits prescriptions and treatments |
| 2005 | RN19_2005_1 | 門診處方及治療明細檔，住院醫療費用清單明細檔，住院醫療費用醫令清單明細檔，特約藥局處方及調劑明細檔，特約藥局處方調劑醫令檔，承保資料 | Patient profiles, Ambulatory care expenditures by visits prescriptions and treatments, Inpatient expenditures by admissions, prescriptions and treatment files |
| 2005 | RN19_2005_2 | 門診處方醫令明細檔 | Ambulatory care expenditures by visits prescriptions and treatments |
| 2006 | RN19_2006 | 門診處方及治療明細檔，門診處方醫令明細檔，住院醫療費用清單明細檔，住院醫療費用醫令清單明細檔，特約藥局處方及調劑明細檔，特約藥局處方調劑醫令，承保資料 | Patient profiles, Ambulatory care expenditures by visits prescriptions and treatments, Inpatient expenditures by admissions, prescriptions and treatment files |
| 2007 | RN19_2007 | 門診處方及治療明細檔，門診處方醫令明細檔，住院醫療費用清單明細檔，住院醫療費用醫令清單明細檔，特約藥局處方及調劑明細檔，特約藥局處方調劑醫令，承保資料 | Patient profiles, Ambulatory care expenditures by visits prescriptions and treatments, Inpatient expenditures by admissions, prescriptions and treatment files |
| *Registry for catastrophic illness (severe mental or physical illness) patients* | | | |
| 1996 | AN8501 | 重大傷病證明明細檔 | Profiles of patients with severe mental or physical illness (as the '**HV**' file mentioned in chapter 6) |
| 1997 | AN8601 | 重大傷病證明明細檔 | Profiles of patients with severe mental or physical illness |
| 1998 | AN8701 | 重大傷病證明明細檔 | Profiles of patients with severe mental or physical illness |
| 1999 | AN8801 | 重大傷病證明明細檔 | Profiles of patients with severe mental or physical illness |
| 2000 | AN8901 | 重大傷病證明明細檔 | Profiles of patients with severe mental or physical illness |
| 2001 | AN9001 | 重大傷病證明明細檔 | Profiles of patients with severe mental or physical illness |
| 2002 | AN9102 | 重大傷病證明明細檔 | Profiles of patients with severe mental or physical illness |
| 2003 | AN9202 | 重大傷病證明明細檔 | Profiles of patients with severe mental or physical illness |
| 2004 | AN9302 | 重大傷病證明明細檔 | Profiles of patients with severe mental or physical illness |

| | | | |
|---|---|---|---|
| 2005 | AN9402 | 重大傷病證明明細檔 | Profiles of patients with severe mental or physical illness |
| 2006 | AN9502 | 重大傷病證明明細檔 | Profiles of patients with severe mental or physical illness |
| 2007 | AN9602 | 重大傷病證明明細檔 | Profiles of patients with severe mental or physical illness |

**Appendix 2 Lists of variables used for the analysis from four main subsets of Registry for beneficiaries ('ID'), Ambulatory care expenditures by visits ('CD'), Inpatient expenditures by admissions ('DD'), Registry for catastrophic illness (severe mental or physical illness) patients subsets ('HV'), and Ambulatory care prescriptions and treatments by visits ('OO')**

| Number | Variable name | English description of the variable |
|---|---|---|
| **Registry for beneficiaries ('ID')** | | |
| 1 | ID | Individual ID number |
| 2 | INS_ID | The ID number of the 'Insured person' |
| 3 | INS_ID_TYPE | Whether the person is the one that pays the premium or is the dependent of 'insured person'. (*so if a person is the dependent, then his ID will not be his INS_ID) |
| 4 | INS_AMT | 'Insured amount': the proxy measure for monthly income |
| 5 | ID_BIRTHDAY | Date of birth |
| 6 | ID_SEX | Gender |
| 7 | INS_RELATION | The relationship with the 'insured person' |
| 8 | AREA_NO_I | The code for place of residence |
| 9 | ID_IN_TYPE | Status of being registered to National Health Insurance |
| 10 | ID_IN_DATE | Date of registration |
| 11 | ID_OUT_TYPE | Status of being withdrawal from National Health Insurance |
| 12 | ID_OUT_DATE | Date of withdrawal |
| **Ambulatory care expenditures by visits ('CD')** | | |
| 1 | FEE_YM | Month and date of the claim |
| 2 | APPL_TYPE | Application made for regular claims or for auditing purposes |
| 3 | HOSP_ID | ID number of the hospital making the claim |
| 4 | APPL_DATE | Date of applying for the claim |
| 5 | CASE_TYPE | Ambulatory care, emergency care, or inpatient care |

| | | |
|---|---|---|
| 6 | SEQ_NO | Sequential number |
| 11 | FUNC_TYPE | Department the ambulatory care visit (eg. cardiology, or psychiatry) |
| 12 | FUNC_DATE | Date of visiting the ambulatory care |
| 13 | TREAT_END_DATE | Date of finishing the ambulatory care visit |
| 14 | ID_BIRTHDAY | Date of birth |
| 11 | ID | Individual ID number |
| 19 | ACODE_ICD9_1 | Main disease code using ICD-9-CM |
| 20 | ACODE_ICD9_2 | Second disease code using ICD-9-CM |
| 21 | ACODE_ICD9_3 | Third disease code using ICD-9-CM |
| 22 | ICD_OP_CODE | Procedure codes using ICD-9-OP-code |
| 23 | DRUG_DAY | Total days of prescriptions |
| 24 | PRSN_ID | ID number of the physician |
| 37 | ID_SEX | Gender |
| **Inpatient expenditures by admissions ('DD')** | | |
| 1 | FEE_YM | Month and date of the claim |
| 2 | APPL_TYPE | Application made for regular claims or for auditing purposes |
| 3 | HOSP_ID | ID number of the hospital making the claim |
| 4 | APPL_DATE | Date of applying for the claim |
| 5 | CASE_TYPE | Ambulatory care, emergency care, or inpatient care |
| 6 | SEQ_NO | Sequential number |
| 7 | ID | Individual ID number |
| 8 | ID_BIRTHDAY | Date of birth |
| 12 | FUNC_TYPE | Department the inpatient admission (eg. cardiology, or psychiatry) |
| 13 | IN_DATE | Date of admission |
| 14 | OUT_DATE | Date of discharge |
| 15 | APPL_BEG_DATE | Start date of the inpatient reimbursement claim |
| 16 | APPL_END_DATE | End date of the inpatient reimbursement claim |
| 17 | E_BED_DAY | Admission days in acute ward |

| | | |
|---|---|---|
| 18 | S_BED_DAY | Admission days in chronic ward |
| 19 | PRSN_ID | ID number of the physician |
| 23 | TRAN_CODE | Result of this admission: 1. discharged; 2. hospitalization continues; 3. change to ambulatory care; 4. Inpatient mortality; 5.Against advice discharge; 6. Transfer to another hospital; 7. Change name; 8. Run away; 9. Committed suicide; 0: others |
| 24 | ICD9CM_CODE | Main disease code using ICD-9-CM |
| 25 | ICD9CM_CODE_1 | Second disease code using ICD-9-CM |
| 26 | ICD9CM_CODE_2 | Third disease code using ICD-9-CM |
| 27 | ICD9CM_CODE_3 | Fourth disease code using ICD-9-CM |
| 28 | ICD9CM_CODE_4 | Fifth disease code using ICD-9-CM |
| 29 | ICD_OP_CODE | Main procedure codes during this admission |
| 30 | ICD_OP_CODE_1 | Second procedure codes during this admission |
| 31 | ICD_OP_CODE_2 | Third procedure codes during this admission |
| 32 | ICD_OP_CODE_3 | Fourth procedure codes during this admission |
| 33 | ICD_OP_CODE_4 | Fifth procedure codes during this admission |
| 70 | ID_SEX | Gender |
| **Registry for catastrophic illness (severe mental or physical illness) patients subsets ('HV')** | | |
| 1 | ID | Individual ID number |
| 2 | DISE_CODE | Disease code using ICD-9-CM |
| 3 | HV_TYPE | Types of severe mental or physical illness |
| 4 | ID_BIRTHDAY | Date of birth |
| 5 | ID_SEX | Gender |
| 6 | APPL_DATE | Date of applying for the claim |
| 7 | APPL_TYPE | Application made for regular claims or for auditing purposes |
| 8 | HOSP_ID | ID number of the hospital making the claim |
| 9 | PRSN_ID | ID number of the physician |
| **Ambulatory care prescriptions and treatments by visits ('OO')** | | |

| | | |
|---|---|---|
| 1 | FEE_YM | Month and date of the claim |
| 2 | APPL_TYPE | Application made for regular claims or for auditing purposes |
| 3 | HOSP_ID | ID number of the hospital making the claim |
| 4 | APPL_DATE | Date of applying for the claim |
| 5 | CASE_TYPE | Ambulatory care, emergency care, or inpatient care |
| 6 | SEQ_NO | Sequential number |
| 8 | DRUG_NO | The number of drug prescribed |
| 9 | DRUG_USE | Drug dose prescribed by the physician |
| 10 | DRUG_FRE | Frequency of drug prescribed |

## Appendix 3 The copy of ethical approval

# 馬偕紀念醫院

## 人體試驗委員會同意臨床試驗證明書

92, Sec.2, Chungshan N. Rd.,Taipei 10449, Taiwan
TEL:+886-2-2543-3535
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台北市中山北路二段 92 號
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查以「嚴重精神疾病患者罹患內外科疾病時所接受的醫療處置調查及研究」試驗案(本會編號:10MMHIS056)，已經本院人體試驗委員會通過，同意吳書儀醫師依所提計劃內容進行臨床試驗，本會組織與執行皆遵ICH-GCP規範，特此證明，有效期限至2011年05月16日。(依照ICH-GCP規定，臨床試驗每屆滿一年，人體試驗委員會必須重新審查是否繼續進行。請於有效期限到期一個月前繳交期中報告以利本會進行審查)。

財團法人台灣基督長老教會
馬偕紀念社會事業基金會

馬偕紀念醫院人體試驗委員會

主任委員 呂 衍 達

2010 年 05 月 17 日

馬偕紀念醫院 M.M.H. 人體試驗委員會 MAY 17 2010 台北市中山北路二段92號

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**Mackay Memorial Hospital**

**Institutional Review Board Approval of Clinical Trial**

17 May, 2010

To Whom It May Concern

**Protocol Title**：Physical health and medical care receipt in people with serious mental illness.
**Protocol Number**：10MMHIS056
**Principal Investigator**：Dr. Shu-I Wu

Above study has been approved by the Mackay Memorial Hospital Institutional Review Board on May 17, 2010 and valid till May 16, 2011. The constitution and operation of this review board are according to the guidelines of ICH-GCP. According to ICH-GCP, IRB will have to review each clinical research case annually and decide whether continue it or not. Therefore, please send us your Annual Report one month before the expiry date.

Yours Sincerely,

Yen-Ta Lu, M.D. Ph.D.
Chairman,
Institutional Review Board,
MACKAY MEMORIAL HOSPITAL,
Taiwan.

# 馬偕紀念醫院人體試驗委員會通知

吳書儀醫師您好：

關於您執行「嚴重精神疾病患者罹患內外科疾病時所接受的醫療處置調查及研究」臨床試驗案(本會編號:10MMHIS056)，經審查後通過，附件為本院人體試驗委員會同意函乙份，請查收。

以下是研究計畫通過審查後，於本院執行**應注意之事項**說明：

1. 請於計畫執行前再次詳閱並遵行『藥品優良臨床試驗準則』。
2. 對於受試者的權益：每一位受試者在進入試驗前都應該獲得詳細的解釋並自願簽署受試者同意書，且每位受試者需持有一份副本，請您及您的研究團隊注意保護他們的隱私。
3. 本會所核發之臨床試驗證明書之效期，會於初審審查時決定，該研究須接受追蹤審查的頻率至少一年一次。
4. 依照 ICH-GCP 規定，臨床試驗計畫執行，每屆滿一年，人體試驗委員會必須重新審查是否繼續進行。請於同意臨床試驗證明書上所載明之有效期限到期一個月前繳交期中報告，以利本會進行審查。
5. 若您期中報告審查通過後，本會將會再發一張同意臨床試驗證明書。
6. 若您有需要變更您的試驗計劃之任何內容(如:修改試驗計劃、變更受試者同意書、新增試驗協同主持人、招募廣告)，均需向本會提出變更申請。在您申請變更獲得核准前，您必須依照原先通過之計畫內容執行或暫停執行。
7. 關於試驗執行中發生之嚴重不良反應（SAE）其規定與通報時程：(依照「**藥品優良臨床試驗準則**」**第 106 條**規定辦理)

| 發生地點 | 通報時程 | 應檢附之文件 |
|---|---|---|
| 總院與各分院 | 1. 死亡或危及生命之嚴重不良事件：獲知日起 7 日內通報。<br>2. 其他非死亡或危及生命之嚴重不良事件：獲知日起 15 日通報 | 1. 本院 SAE 通報表<br>2. 衛生署 SAE 通報表格<br>3. 病歷摘要 |
| 國內其他醫院 | 獲知日起 15 日內提供詳細書面資料 | 1. 本院 SAE 通報表<br>4. 衛生署 SAE 通報表格<br>2. 病歷摘要 |

| | | |
|---|---|---|
| 國外之試驗機構 | 獲知日起 30 日內通報 | 1. 通報之 SAE 個案清單<br>2. 多國多中心計畫之 SAE 通報表。<br>3.CIOMS Form(或其他相當之表格) |

8. 在試驗計畫執行期間，若因故需提前中止/終止，請您向本會提出中止/終止之申請，並繳交試驗報告。
9. 在試驗計畫執行結束後，須請您提交結案報告。
10. **試驗執行期間，您所收納之受試個案其因試驗而產生之費用須由試驗委託者負擔，本院人體試驗委員會將給您此計畫專用之學術減免單，於收到學術減免單後始可使用，本會將依此進費用行核銷作業。**
11. **對於臨床試驗所需之藥品，僅可由本院藥局、試驗主持人及研究護士保管與發放，唯試驗藥品應妥善保管，發放藥品予受試者應重複核對，以善盡保護受試者之責。**
12. 臨床試驗相關之申請表格，請參考本院人體試驗委員會之網頁，網址為『http://www.mmh.org.tw/taitam/irb/index.htm』

以上，若您於試驗執行期間有任何問題，請與人體試驗委員會祕書處聯絡，謝謝~~

**聯絡資訊: 陳婉婷小姐(分機: 3486)、徐珮珊小姐(分機: 3487)**

馬偕紀念醫院 M.M.H. 人體試驗委員會 MAY 17 2010 台北市中山北路二段92號

**馬偕紀念醫院人體試驗委員會**

2010.05.17